TRENDS AND BARRIERS TO HCV TREATMENT IN THE ERA OF DIRECT ACTING ANTIVIRALS AMONG PEOPLE WHO INJECT DRUGS IN BALTIMORE, MARYLAND

by

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Abstract

Background: Hepatitis C virus (HCV) infection is the most prevalent bloodborne viral infection nationally. Injection drug use is the most commonly reported mode of transmission and incident cases of acute HCV infection have more than quadrupled between 2010 and 2018. This increase is primarily attributed to shared injection practices associated with the nation's opioid epidemic. Effective treatment for HCV emerged in late 2013 via the advent of direct acting antiviral (DAA) agents, but treatment rates remain exceedingly low among PWID. Our understanding of barriers to treatment among PWID is based largely on studies conducted in the pre-DAA era when treatment itself was a barrier. Our study aims to evaluate how HCV treatment uptake has changed since the availability of DAAs among a community-based cohort of current and former PWID with the goal to better understand potential barriers to DAAs and subgroups of PWID at-risk of not accessing treatment today.

Methods: We conducted our research using data from the ALIVE (AIDS Linked to the IntraVenous Experience) study, a community-based cohort of PWID, ongoing since 1988, located in Baltimore, MD. Aim 1 identified clusters of low HCV treatment penetration in Baltimore, MD at three time-points: the interferon-era (2006-2007), early DAA-era (2015-2016) and later DAA-era (2017-2018). Subsequently, we evaluated whether these areas are best explained by neighborhood deprivation or individual characteristics. Aim 2 evaluated differences in knowledge of HCV and its treatment by HCV and HIV infection status and other individual-level factors. We used a subset of questions from a 17-question survey, performed at enrollment among participants enrolled 2015-2018 to create three HCV knowledge subscales: transmission, natural history, and treatment. Aim 3 evaluated temporal changes in HCV treatment uptake from 2011-2019 to identify groups with persistent low treatment uptake and associated correlates.

Results: In our first aim, we identified clusters of HCV viremia in two of the three time-periods. The first, was a single cluster in the interferon-era (2006-2007) and then two clusters in the early DAA-era (2015-2016). No cluster was identified in the late DAA-era. While characterizing these clusters, we found that neighborhood deprivation was the primary predictor of clustering in both eras. In Aim 2, we found that, overall, HCV knowledge was high among these PWID but there was variability in treatment knowledge. We found higher treatment knowledge was associated with being HCV mono-infected, compared to HCV-negative PWID and among participants who were aware of their HCV diagnosis before completing the HCV assessment compared to those diagnosed through testing at the ALIVE study. Finally, in Aim 3 we found that treatment uptake improved greatly after DAAs became available. Improved treatment uptake in the early DAA-era was associated with older age, healthcare utilization, and having cirrhosis. Healthcare utilization and high frequency drug use were the predictors of treatment uptake in the late DAA-era.

Conclusions: We found that, overall, treatment uptake had improved between the interferon and DAA eras but was slower in areas of higher neighborhood deprivation. Our failure to identify clusters of HCV treatment need in the late DAA-era suggests that treatment has likely penetrated even the most marginalized areas. We evaluated changes in HCV knowledge, a known individual-level barrier in the interferon-era and found variability in treatment knowledge. Results suggest that information regarding treatment is probably communicated when a person is diagnosed or at some point afterwards. However, results also showed that residual misinformation regarding interferon-based therapies persist today, particularly knowledge of side effects, pill burden, and treatment duration. Subgroups at-risk of poor treatment uptake today were individuals not engaged in healthcare or injecting drugs with high frequency. These subgroups might be difficult to reach and targeted approaches will be needed to engage these individuals.

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Chapter 1. Introduction and Background

Specific Aims

With 4.1 million people having been infected with the hepatitis C virus (HCV), HCV is the most common bloodborne viral infection in the United States. Moreover, there is growing concern because HCV incidence has increased more than 4.1-fold since 2010, with most of the cases among young people who inject drugs. Furthermore, HCV-related mortality is also increasing among an aging population some of whom were PWID who were infected decades ago.

New treatment options, direct acting antivirals (DAA), became available in late 2013. These require only a single pill per day, for less than 12 weeks with high cure rates. This replaced interferon-based therapies as the standard of care, which included weekly injections, high pill burden for 48 weeks, and cure rates of about 50%. Because of the growing burden of HCV incidence and mortality, and availability of DAAs, both the World Health Organization and National Academies of Sciences, Engineering, and Medicine released two goals to achieve HCV elimination by 2030. They are to decrease HCV incidence by 90% and HCV-related mortality by 65%.

Since then, HCV treatment uptake has increased remarkably, but remains low among some subgroups including PWID. Barriers to HCV treatment before DAAs were well understood, with the primary barrier being side effects related to the treatment itself. Additional research is needed to understand the structural and individual barriers preventing PWID from being treated today, in the era of DAA-based therapy. It is particularly important to understand differences across key subgroups to provide insight into the efforts to universally expand

HCV treatment among PWID. To contribute to these efforts, we propose the following specific aims:

Aim 1: To identify clusters of low HCV treatment penetration in Baltimore City and Baltimore County, Maryland and evaluate how these clusters have evolved over time. We will use serial cross-sectional data from the ALIVE study to explore the spatial distribution of HCV treatment need and identify statistically significant clusters of PWID with poor treatment uptake for three time-periods settings. These include the interferon-era (2006-2007), in which HCV treatment uptake was low, early in the availability of DAAs (2015-2016), and later in the availability of DAAs (2017-2018). Subsequently, we will examine how features of the underlying population and neighborhood deprivation explain the observed clustering. *We hypothesize that clusters of persons who need HCV treatment will change over time and be areas with of high neighborhood deprivation.*

Aim 2: To evaluate differences in knowledge of HCV and its treatment by HCV and HIV infection status and other individual-level factors. We will use cross-sectional data to determine the extent to which knowledge regarding HCV treatment has penetrated the PWID community and how it varies by both HCV and HIV status, and proximity to service locations, including substance use treatment facilities, where PWID could potentially receive HCV education. We will do this by analyzing data from ALIVE participants recruited into the community-based cohort of PWID from 2015-2018. Domains of interest included knowledge of HCV transmission, natural history, and treatment modalities. *We hypothesize that HCV knowledge will highest among HIV/HCV coinfected compared to HCV mono-infected and HCV uninfected PWID.*

Aim 3: To compare temporal changes in HCV treatment uptake from 2011-2019 among PWID and identify groups with persistent low treatment uptake and associated correlates. We will use longitudinal data to understand changes in HCV treatment uptake before and after the availability of DAAs among PWID in the ALIVE study. Furthermore, we will evaluate how barriers and facilitators of HCV treatment have changed over time and identify groups that have lower than expected treatment uptake today. *We hypothesize that uptake will be highest among coinfected HIV/HCV PWID with HIV viral suppression and vary by age, and duration of drug use.*

We plan to nest these specific aims within the ALIVE (AIDS Linked to the IntraVenous Experience) study, a community-based cohort of former and current PWID, in Baltimore City, ongoing since 1988. Baltimore is a unique setting in which to examine the changes in HCV treatment among PWID due to its longstanding population of people who inject heroin and high HCV prevalence and incidence among PWID. The expected outcomes of this study will be findings to inform local HCV elimination efforts on where and how to engage and treat HCV in HIV/HCV coinfected and HCV mono-infected PWID.

Hepatitis C Virus (HCV)

Isolated in 1989, HCV is a small, enveloped, positive sense single-stranded RNA virus in the Flaviviridae family. It is comprised of a lipid envelope, two envelope proteins, and a nucleocapsid, which contains the viral genome that encodes the structural and non-structural proteins of HCV. The structural proteins are used to form the capsid and two envelope proteins of future virions. The six non-structural proteins, NS2, NS3, NS4A, NS4B, NS5A, NS5B, form the replication complex that will make more positive single-stranded RNA, which will be packaged into viral particles with the structural proteins.

HCV has a high amount of genetic heterogeneity. To date, eight genotypes and over 100 subtypes have been discovered.[1,2] Furthermore, once infected, intrapersonal mutation is common.[2] There is substantial variation in the global distribution of genotypes. For example, genotype 1 is most common in North America and Europe, comprising 75% and 64% of all cases of HCV, respectively.[3] Whereas, genotype 4 accounts for 65% of the infections in North Africa and the Middle East and more than one-third of the cases in the Asia-Pacific region are genotype 3.[3] Given the heterogeneity of the virus itself and global epidemiology, a single, universal HCV vaccine has yet to be approved by the FDA. However, both prophylactic and therapeutic vaccine trials are underway.

Natural History and Symptomatology

Of those who develop acute HCV, between 55% and 85% will progress to chronic infection, which is defined as the persistence of HCV RNA in blood for at least 6-months.[4,5] High rates of spontaneous clearance are associated with being female, white, a younger age at time of infection, low HCV viral load, abstinence from alcohol and injection drug use, HIV coinfection, and ILB28 genotype CC.[4,6–11] Over the next 25-30 years, between 20% and

30% of those with chronic HCV will develop cirrhosis.[4] Among those who develop cirrhosis, 30% will develop hepatic decomposition over 10 years, which has a 5-year survival rate of 50%, or develop hepatocellular carcinoma (1%-4% per year).[4,12] However, HCV sequalae is impacted by a variety of host, viral, or environmental factors. For example, older age at infection, obesity, alcohol use, HIV coinfection, genotype 1, and high HCV viral load have been associated with accelerated progression of fibrosis.[11–14] But encouragingly, studies have shown that liver damage, even cirrhosis, is reversible after a person is successfully treated for HCV.[15,16]

HCV's average incubation period is 14-84 days but can last up to 128 days.[17] However, few individuals with acute HCV infection ever experience symptoms.[11,18] If they do, symptoms are non-specific and include flu-like symptoms, abdominal pain, fatigue, nausea, and jaundice.[4,11] As a result, early detection of HCV is very difficult. Most people become symptomatic decades after being infected when they begin to experience HCV-related morbidity. These patients may exhibit physical signs of chronic liver disease and decompensated cirrhosis, like jaundice, portal hypertension, esophageal varices, or ascites.[19,20]

HCV Diagnostics and Liver Fibrosis Staging

Initial screening for HCV infection is typically done with a serologic assay used to identify antibodies that indicate if a person has been exposed to HCV. The two serologic tests used in the United States are an enzyme immunoassay (EIA) and point-of-care rapid immunoassay. Sensitivity and specificity of the EIA test are roughly >98% and 100%, respectively.[21] A pooled analysis found that the combined sensitivity of the point-of-care tests ranged from 86.2% to 99% but all had a

specificity of >99%.[22] Among those with a reactive serologic test, a confirmatory molecular HCV RNA test is required to determine if the person has spontaneously cleared the virus, has active infection, or was a false positive.[12,23] The real-time polymerase chain reaction (PCR) HCV RNA test is able to detect a minimum RNA level of 10-50 IU/mL, giving it good sensitivity. Additionally, the test's specificity is 98%-99%.[12] Commercial laboratories now offer reflexive HCV RNA testing, which enables the laboratory to automatically perform the confirmatory HCV RNA test on any reactive HCV serologic assay. This enables healthcare providers to disclose a confirmed HCV test result at a single visit, rather than over two with a second venipuncture.

In 2013, the Centers for Disease Control and Prevention (CDC) updated their testing sequence.[24] With the updated algorithm, persons that have a negative antibody test are not HCV infected, unless there is reason to believe the test was a false negative, like suspected acute infection or if the individual is immunocompromised.[24] Positive HCV antibody and RNA tests indicate active, chronic, infection, and the person should be linked to HCV care.[24] Finally, an HCV positive antibody but negative HCV RNA test could indicate one of three things: successful cure, spontaneous clearance, or false positive.[24] If indicated, a different antibody assay could be used to differentiate between past infection and a false positive test.[24]

Once a person with chronic HCV infection is engaged in HCV care, staging of liver fibrosis is used to assess HCV-related morbidity.[12] There are a number of scoring systems used to quantify liver fibrosis. One that is frequently used is the METAVIR score.[25] It categorizes liver fibrosis into five stages of increasing severity: none (F0), mild (F1), moderate (F2), severe (F3), and cirrhosis (F4).[26] A liver biopsy is the gold standard for directly evaluating liver fibrosis.[27,28] However, biopsies are invasive and there are questions regarding its

reliability due to sampling error.[28,29] Therefore, noninvasive methods to estimate liver fibrosis, like biomarkers and elastography, are also available and used widely today.

Indirect biomarkers use a combination of laboratory tests, like platelets, aminotransferase (AST), and alanine aminotransferase (ALT), to estimate liver fibrosis. Two of the most commonly used to predict advanced fibrosis or cirrhosis include aspartate aminotransferase-to-platelet ratio index (APRI) and FIB-4.[28] Both use a patient's AST and platelet count, but the FIB-4 also uses patient age and ALT levels.[28] These indirect methods are better at confirming advanced liver disease but are less reliable at differentiating intermediate fibrosis.[28] For example, in detecting moderate fibrosis (F2), the APRI had a sensitivity of 84% and specificity of 41%. In diagnosing cirrhosis (F4), the sensitivity decreased to 54% but specificity increased to 78%.[28] Therefore, it is suggested that providers use additional methods to predict liver fibrosis when using indirect markers of fibrosis.

Finally, transient elastography offers a direct, noninvasive alternative to confirm liver fibrosis. It is an ultrasound-based method used specifically for the purpose of determining liver fibrosis. Transient elastography works by emitting a shear wave through the liver via an ultrasound transducer probe mounted on a vibrator.[30] The velocity of the shear wave is used to determine the stage of liver fibrosis, measured in kilopascals.[30,31] Compared to other noninvasive methods to measure liver fibrosis, transient elastography is one of the most accurate and reliable ways to estimate a METAVIR fibrosis score. For example, in diagnosing cirrhosis, transient elastography has a sensitivity and specificity of 95%, greatly surpassing that of other noninvasive methods. Specifically among a cohort of people who inject drugs, the cut-offs for significant fibrosis and cirrhosis were 9.3 and 12.3, respectively, which have a sensitivity of 86% and 75% and specificity of 75% and 86%, respectively.[32]

HCV Transmission and Prevention

HCV is transmitted primarily through percutaneous exposure to contaminated blood. Consistently, the most common mode of transmission has been shared injection drug use (IDU) practices.[23,33,34] However, at its highest in 1982, non-A, non-B hepatitis transmission through blood transfusions accounted roughly 17% of all HCV cases, a percentage similar to those attributed to injection drug use.[33] The percentage of transmission-related cases dropped to 6% in 1988, which was prior to the implementation of HCV antibody testing of blood donations, but did align with changes in the donation practices to decrease HIV transmission.[33] Routine screening was implemented in 1990 and by 1994, counties that were part of the sentinel viral hepatitis surveillance system failed to identify a single case attributed transfusion-related transmission.[23]

While transfusion-related transmission decreased, IDU-related transmission increased from roughly 20% in 1982 to 60% by 1998.[23,33] It has likely increased even more, since the percentage of incident cases of acute HCV that report IDU as the primary risk exposure increased to 75% in 2011 and 82% in 2018.[17,35] Per-event probability of transmission through shared drug use is estimated to be 0.57% but could be up to 6%, depending on prevalence of HCV in the injecting equipment.[36] However, other sources of ongoing transmission remain, albeit contributing a far lesser extent to overall transmission. They include intranasal drug use, receiving a tattoo or piercing from unlicensed locations that reuses needles, nosocomial occupational exposures, being born to an HCV-positive mother, and through household contact, like sharing toothbrushes, razors, or diabetic needles.[35]

Despite the lack of availability of a prophylactic vaccine, highly effective prevention measures are available. For example, primary prevention strategies used to reduce the risk of acquiring HCV initially included routine HCV screening of blood donations and expansion of syringe services programs to decrease the repeat usage of injection paraphernalia.

However, since the availability of direct acting antiviral (DAA) HCV treatment medications in late 2013, “treatment as prevention,” a concept borrowed from HIV, is also applicable to HCV. The goal of secondary and tertiary prevention methods has been to improve detection to reduce the risk of HCV-related morbidity and mortality. To do this, the CDC has expanded their testing recommendations. The initial 1998 CDC testing guidelines recommended screening of the highest-risk individuals, listed in Table 1.[23] In 2012, the CDC updated the guidelines to include one-time testing among all individuals born between 1945 and 1965, as that age cohort comprised 75% of all HCV cases.[37] Finally, in 2020, they were updated once again to recommend one-time testing on all individuals ≥18 years of age and pregnant women.[34] Furthermore, as HCV treatment medications improved, the CDC also updated their testing algorithm in 2013 to facilitate better linkage to treatment.[24]

Table 1. Criteria for HCV Antibody Testing Based on 1998 CDC HCV Testing Recommendations*
History of injection drug use, even once or many years ago
Received clotting factor concentrates produced before 1987
Was placed on long-term hemodialysis
Has persistent abnormal alanine aminotransferase levels
If they were notified that they received blood from a donor who was later diagnosed with HCV
Received a transfusion of blood or its components before July 1992
Received an organ transplant before July 1992
Nosocomial needlestick, sharps or mucosal exposure to HCV-positive blood
Child born to an HCV-infected mother

*Adapted from the 1998 CDC Recommendations for Prevention and Control of Hepatitis C Virus Infection and HCV-Related Chronic Disease

HCV Treatment Modalities

HCV is a curable viral infection. The goal of HCV treatment is eradication of the infection (“cure”), which is defined as a sustained virologic response (SVR) indicating the absence of HCV RNA in serum at least 12 weeks after the end of treatment.[5] There have been tremendous advances in HCV treatment, since it was first discovered that non-A, non-B

hepatitis was curable in 1986. The history of HCV treatment modalities can be broadly organized into two eras, the interferon-era (1986-2013) and direct acting antiviral (DAA) era (2014-2020).

Interferon Era of HCV Treatment

Interferon (INF), found naturally in the human body, stops viral replication by both non-viral specific and viral specific immune responses that kill infected cells.[38] The interferon-era of HCV treatment is known for long durations of complicated treatment regimens, drug-related adverse side effects, food restrictions, and poor overall cure rates. Additionally, not only did treatment outcomes vary by a variety of factors, including genotype, and evidence of cirrhosis, but there were numerous contraindications for treatment due to drug-drug interactions or side effects.

The first FDA-approved treatment was interferon-alfa monotherapy administered using subcutaneous injections 3-times per week.[38] Initially, treatment lasted for 6-months, with 6% of patients achieving SVR.[5,38] Subsequently, treatment was extended to 12-months and SVR rates increased to 16%.[5,38] Adding ribavirin was an early breakthrough that more than doubled cure rates, reaching 42%.[5] In 2001, interferon-alfa was pegylated, which increased its half-life and decreased the number of weekly injections from three to one.[5,38] However, SVR rates varied greatly by genotype, prior treatment experience, and evidence of cirrhosis.[5,12,39] For example, SVR rates of genotypes 2 and 3 were as high as 80%, which was almost twice the SVR rates for genotype 1.[5] Finally, with the FDA-approval of two protease inhibitors, boceprevir and telaprevir, in 2011, SVR rates exceeded 60% among some subgroups.[38,39]

Adverse events were common in the interferon-era. In fact, roughly 75% of all patients who were on interferon-based therapy experienced at least one side effect.[5] The most common

one was anemia since it was associated with all medications. But it was a major concern for those on ribavirin, as it was associated with severe anemia.[5,38] Adverse events for interferon-alfa were also severe. They ranged from flu-like symptoms to depression and even life-threatening hepatic decompensation for those with cirrhosis.[5,38] In fact, because of those side effects, treatment was contraindicated for those with uncontrolled depressive symptoms because it could increase the risk of suicide.[5]

Interferon-based therapies also had high pill burden. For example, treatment guidelines from the American Association for the Study of Liver Diseases (AASLD) recommended that individuals with genotypes 1 and 4 receive weekly peginterferon injections plus ribavirin using weight-based dosing, which could be up to 6-pills daily, for 48 weeks.[5,12,39] For genotypes 2 and 3, AASLD recommended weekly peginterferon injections with a lower fixed dosage of ribavirin for 24 weeks.[5,12,39] The updated guidelines in 2011 added both telaprevir and boceprevir to treatment recommendations, which increased the number of pills taken daily by 6- or 8-pills, depending on the medication.[39] Going into the DAA-era, treatment-naive patients, without cirrhosis, weighing >165 pounds (75 kg) with genotype 1, the most common in the US, took 12 or 14 pills daily and received weekly injections of interferon for up to 48 weeks.[39]

Direct Acting Antiviral Era of HCV Treatment

Direct acting antivirals work by targeting nonstructural proteins involved in the HCV life cycle. The major classes are NS3/NS4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors. The first two, simeprevir and sofosbuvir, were approved by the FDA in late 2013. However, sofosbuvir, specifically, was the breakthrough of DAA HCV treatment medications. It is a nucleotide analog inhibitor of NS5B polymerase that was approved by the FDA to be taken in combination with peginterferon-alfa and ribavirin to treat genotypes 1-4.[40,41] It is a single, well tolerated pill, taken once daily for between 12 and 24 weeks and

cure rates were >90%.[40] Adverse events were attributed to the other medications but could include headache or fatigue.[41] In November 2014, it was approved by the FDA to be used in combination with simeprevir to treat genotype 1, as the first all-oral, interferon-free HCV treatment regimen.[42–44]

For the first 2-years of the DAA-era, HCV treatment regimen and response still varied by genotype and even subtype. For example, the 2015 AASLD HCV treatment guidelines recommended that patients with genotypes 1, 4, 5, or 6 take a single pill for 12 weeks.[42] Patients with genotypes 2 or 3 also took weight-based ribavirin and in some cases, interferon.[42] A key game changer in HCV therapeutics was the approval of a pangenotypic fixed-dose pill, sofosbuvir-velpatasvir, which was FDA approved in 2016.[45] Furthermore, SVR rates were >95%, regardless of liver fibrosis stage or prior HCV treatment experience.[46,47] Since then, more pangenotypic medications have become available. In fact, today, treatment requires a single pill, taken daily for 8-12 weeks, with cure rates >98%.[48] Additionally, HCV treatment no longer requires food restrictions and there are minimal adverse events, drug-drug interactions, or contraindications for treatment.[48]

When it was approved, sofosbuvir cost $1,000 per day or $84,000 for a 12-week course.[49] In response, State Medicaid plans and Managed Care Organizations quickly implemented insurance restrictions that barred access to DAAs. Early restrictions included documentation of advanced liver fibrosis or cirrhosis, confirmation that the patient abstained from any drug use for up to 12 months, and requiring that only hepatologists, gastroenterologist, or infectious disease specialists could prescribe treatment. But these vary by state. For example, in 2014, 74% of the states required that patients have documentation of advanced liver fibrosis (METAVIR F3) or cirrhosis (METAVIR F4) to be approved for treatment.[49] By 2017, no states required a patient have cirrhosis but 23% still required documentation of advanced liver fibrosis.[50] However, this decreased to 8% in 2019.[51] Conversely the

percentage of states with no fibrosis restrictions rose from none, in 2014, to 35%, in 2017, and 79%, in 2019.[49–51] Similar trends were seen with the sobriety restriction, which went from 100% requiring abstaining from substance use for up to 12 months to 36% requiring abstaining for substance use for up to 6 months.[49,51] And today, only Arkansas requires that a specialist of prescribe HCV medications.[51]

HCV Treatment among Key Populations

HCV Treatment among Persons with HIV/HCV Coinfection

A variety of factors influence the clinical course of HCV, but HIV/HCV coinfection is particularly important. Roughly 25% of all HIV-positive individuals in the United States are coinfected with HCV. However, among PWID, upwards of 90% of all HIV-positive PWID are coinfected with HCV.[52] Coinfected individuals are at an increased risk of HCV-related mortality; a number of studies have demonstrated that progression to liver diseases, like cirrhosis, is accelerated by HIV.[53] In fact, coinfection increases a person's risk of cirrhosis two-fold.[53,54] Today, HCV-related liver disease is one of the leading non-AIDS causes of death among people living with HIV.[55,56] As a result, HCV treatment guidelines prioritized treatment among coinfected individuals.[12,42] However, treatment of coinfected individuals in the interferon-era was complicated by toxicity concerns due to drug-drug interaction between antiretroviral and antiviral treatments, lower SVR rates among those who were treated, and exacerbated side effects, like ribavirin-related anemia.[12,54] As a result, in the interferon-era, less than 5% of coinfected patients were treated.[57,58] By comparison, today's treatment regimens have shown no differences in SVR rates by HIV coinfection, no additional side effects, and fewer drug-drug interactions between antiretrovirals medications

and DAAs.[59,60] As a result, treatment uptake has been better in HIV/HCV coinfected patients than HCV mono-infected.[61]

HCV Treatment and Reinfection among Persons who Inject Drugs (PWID)

Studies have already shown that treatment efficacy and SVR rates of both interferon-based and DAAs do not vary by drug use.[62–65] However, some medical providers may still be reluctant to treat active PWID due to concerns of nonadherence and/or reinfection.[66–69] In the interferon-era, studies failed to show significant differences in adherence to HCV treatment among PWID.[65] For example, in one study, the overall rate of nonadherence was 8.4% among those who used drugs, compared to 6.8% in those who did not.[65] Moreover, studies in the DAA-era have shown excellent adherence to these shorter, simpler treatment regimens.[62,70]

Even though HCV is curable, reinfection is possible. Studies in the DAA-era found that reinfection among people who have recently used drugs can range from none to over 20.0 per 100 person-years.[71–74] However, reinfection rates are lower among PWID who are engaged in harm reduction services.[72,73] Despite the risk of reinfection, treatment guidelines consider PWID a high priority population. Similar to treatment as prevention (TasP) for HIV transmission, scaling up HCV treatment among PWID is an effective method to lower community load.[75] This would, thereby, decrease HCV incidence and, by extension, prevalence, even if risk behaviors remain.[76,77]

Epidemiology of HCV and Calls for HCV Elimination

The hepatitis C virus (HCV) is the most prevalent bloodborne viral infection in the United States.[23,37,78,79] Currently, it is estimated that 4.1 million people have been infected with HCV, of which 2.4 million have current HCV infection.[79] At its peak, in the 1980s and early

1990s, the CDC estimated that there were, on average, 230,000 incident cases of acute HCV infection annually.[23] These cases were primarily associated with shared risk behaviors among groups impacted by the nation's cocaine and heroin epidemic in the 1980s and 1990s.[33] These cases were among Black individuals and persons between the ages of 30-49 years.[23] Most were unaware of their HCV infection and as these individuals aged, they began to experience the downstream effects of HCV that were associated with HCV-related morbidity and mortality.[80] In fact, in 2007, HCV-related deaths exceeded those attributed to HIV.[81] In 2013, they exceeded those attributed to the 60 other reportable infectious diseases combined, making it the leading cause of death due to an infectious disease in the United States.[82] By the time that DAAs became available, HCV was the leading cause of end-stage liver disease, hepatocellular carcinoma and cirrhosis; as well as, the primary indicator for liver transplantation in the United States.[40,83–85]

HCV incidence dropped sharply, starting in 1992 after the implementation of primary prevention measures for HCV and HIV and expanded awareness of HCV risk factors. However, starting in 2003 the number of reported cases of acute HCV infection stabilized until 2010, when HCV incidence began to increase again.[86] In fact, the reported number of cases of acute HCV infections increased 4.1-fold between 2010 and 2018 to an estimated 50,300 new infections in 2018.[17,86] Similar to the 1980s and early 1990s, these cases are primarily among young individuals between the ages of 20-39 years.[17] But they are also white, female, and live in suburban and rural areas of the United States, consistent with demographic groups impacted by the nation's opioid epidemic.[17,87–89] Because of the DAAs and the epidemiology of HCV, in 2015, the World Health Organization (WHO) and National Academies for Sciences, Engineering, and Medicine released two goals to eliminate HCV by 2030. They were to decrease incidence by 90% and mortality by 65%.[90]

Progress Towards HCV Elimination in the United States

Progress has been made particularly on the mortality goal. The estimated number of people with chronic HCV infection decreased from 3.4 million in 2010 to 2.4 million in 2016.[78,79] In fact, the overall age-adjusted HCV-related mortality rates peaked at 5 deaths/100,000 population in 2014 and then decreased 26% to 3.7 deaths/100,000 population in 2018.[17,20] This was even more pronounced among those aged 55-64 years, the group with the highest mortality rate. At its highest in 2013, there were 25.2 deaths/100,000 population, which decreased to 17.3 deaths/100,000 population in 2018.[17,20] Modelling done by the Polaris Observatory in 2020 confirmed this progress, estimating that the US would reach the HCV mortality goal by 2023, despite only successfully treating 40% of all HCV-infected individuals today.[91]

By contrast, the Polaris Observatory found that the US is not on track to decrease HCV incidence by 90%.[91] To achieve this goal, efforts must be made to improve HCV detection but also linkage to HCV treatment. The expansion of the CDC testing guidelines to perform universal testing on all over the age of 18 years, which augment routine testing already performed at services used by PWID, will improve the number of PWID who are aware of the diagnosis.[34,92] However, this population faces a number of barriers to treatment. Reasons for poor HCV treatment uptake in the interferon-era were well characterized and included structural, provider, and individual-level barriers. The primary barrier to HCV treatment in the interferon-era was treatment itself, either low knowledge or fear of side effects.[93–100] But medical providers were also reluctant to treat PWID due to stigma related to substance use, and concerns over non-adherence or reinfection.[67,69,99,101,102] Additionally, non-specific barriers, like distrust of the healthcare system and insurance coverage, were also reasons why PWID chose to not receive HCV treatment.[101,102]

Since interferon-based treatments have been rendered obsolete, the primary barrier to HCV treatment has been removed. However, treatment uptake among PWID in the DAA-era remains low, overall. In fact, between 2015 and 2017, it was estimated that only 16% of PWID were treated with DAAs.[77,103] It is clear that barriers remain. This proposal focuses on the identification of key barriers to HCV treatment uptake in the DAA era, including knowledge and other individual and structural barriers to engagement against a backdrop of a shifting epidemiology of drug use.

HCV and PWID in Baltimore, Maryland

With the highest number of PWID per capita in the country, Baltimore City has an established heroin epidemic that is exacerbated by prescription drug use and fentanyl.[104] In 2018, 89% of Maryland's overdose deaths were opioid-related.[105] In Baltimore City, the number overdose deaths increased 100% from 2015-2018.[105] The effects of this widespread drug use are reflected in the city's burden of HIV and HCV. Nationally, in 2016, <6% of HIV prevalence was attributed to IDU.[106] Whereas, up to 30% of all HIV-positive residents of Baltimore reported IDU as the mode of transmission.[107] HCV prevalence among PWID peaked at 93% in 1993 and remained high even as the overall incidence of acute HCV declined around the US.[108,109] Finally, HCV treatment has increased markedly in Baltimore, but it is unclear if all groups are reached, notably PWID actively injecting or living outside of the city.[110]

AIDS Linked to the Intravenous Experience (ALIVE) Study

ALIVE is an ongoing prospective cohort of current and former PWID, ongoing since 1988.[111] Originally started to understand the natural history and incidence of HIV among PWID,

ALIVE is a seminal study that has helped to inform understanding of the epidemiology of HIV and HCV among PWID. The ALIVE study has contributed to our current understanding of the prevalence and incidence of HCV among PWID, uptake of HCV treatment and barriers to treatment in the interferon era. A 2008 study found that among ALIVE participants only 5% initiated HCV treatment and <1% were successfully cured.[96] This was explained, in part, by low HCV knowledge and fear of treatment, consistent with other studies at the time.

As a community-based cohort, participants are recruited independent of engagement in health or harm reduction services, through street outreach, flyer distribution, and peer referrals. ALIVE has maintained excellent follow-up rates, where 5% are lost-to follow-up and 2-3% die annually. As a result, ALIVE is comprised of individuals representative of the PWID community in Baltimore.

Recruitment has spanned more than 3 decades and five cohorts: 1988-1989 (N=2,946), 1994-1995 (N=434), 1997-1998 (N=295), 2005-2008 (N=1,009), and 2015-2018 (N=674). Eligible participants are ≥18 years of age with a history of IDU. In total, 5,358 individuals have been enrolled in ALIVE. For the first 20 years, participants have been older and non-Hispanic Black.[112] For example, in the original cohort, >92%% of the participants were Black and the median age was 51 years (IQR: 45 years, 54 years). But over the past 10 years, there was a shift in the demographics to include a younger and non-Hispanic white population. By comparison, in the most recent cohort 65% of the participants were Black and the median age dropped to 45 years (IQR: 33 years, 55 years). In fact, among non-Hispanic white participants recruited in the 2015-2018 cohort, 50% were between the ages of 18-34 years. Over ALIVE's 30-year study period, only a few participants were of Hispanic heritage. Prevalence of HCV and HIV/HCV coinfection has dropped slightly but remained high. In the 1988 cohort, roughly 85%-90% had HCV infection and 95% were coinfected with

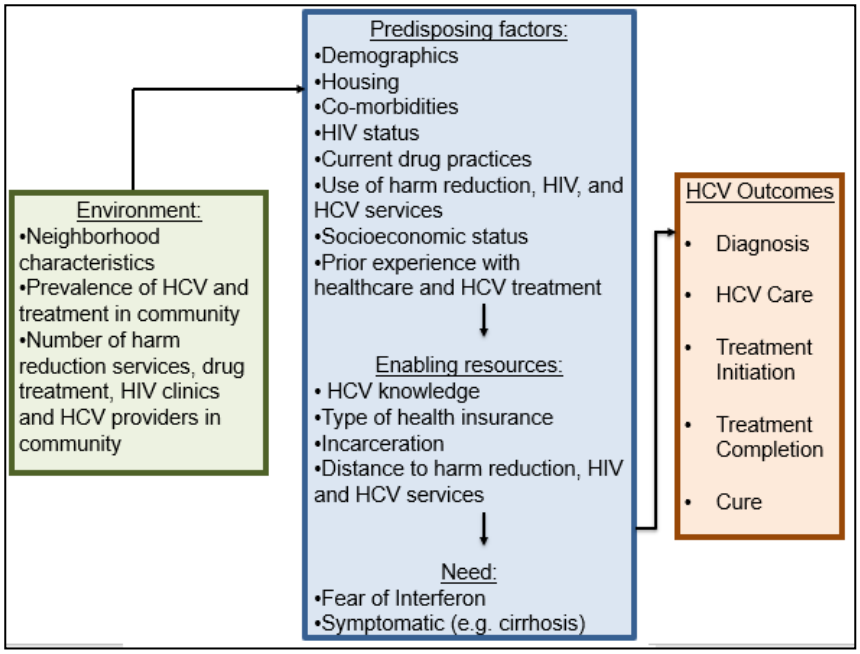
HIV. In the most recent cohort, 70%-75% had HCV infection and 85% were coinfected with HIV. Finally, 15% of ALIVE participants live in counties surrounding Baltimore City. As a result, we have representation reflective of both a historical urban minority focused epidemic and an emerging epidemic that includes suburban areas and broader racial representation.

At the baseline visit, ALIVE participants self-report demographic characteristics, drug use, and medical history. Participants are asked a series of questions to assess HIV and HCV knowledge, after which they are counseled regarding both diseases. At semi-annual visits, participants are asked about drug use, comorbidities, healthcare utilization, and report frequency of IDU within the past 30 days. Additionally, participants provide updated contact information, like residential address that is geocoded, and a FibroScan is performed to measure liver fibrosis.[113] All questionnaires have been developed through focus groups with participants from the ALIVE community advisory board and collaborations with research on similar populations of PWID to those found in Baltimore. They are then pilot tested and modified based on the feedback from trained interviewers and participants. Participants are screened for HIV at each study visit using an enzyme-linked immunosorbent assay (ELISA) and Geenius HIV 1/2 Confirmatory Assay (Bio-Rad, Hercules, California). An HIV RNA test (Roche, Basel, Switzerland) is performed on HIV-positive participants at each visit to determine HIV viral suppression (≤50 copies/ml). All participants are screened for HCV antibodies using an ELISA (Ortho Clinical Diagnostics, Raritan, NJ) and confirm chronicity using an HCV RNA test (Abbott Molecular, Des Plaines, Ill). HCV RNA testing is conducted annually with additional testing to confirm cure among participants who self-report initiating HCV treatment between visits. Given the breadth of data, diversity of participants, location in Baltimore, and prior research in barriers to HCV treatment, ALIVE is an ideal in which to nest this research.

Conceptual Framework

Our conceptual framework (Figure 1), adapted from Andersen's behavioral model for healthcare utilization, hypothesizes that HCV treatment uptake among PWID is influenced by the contextual environment, as well as, a confluence of individual factors conceptualized as predisposing factors (demographics that change a person's likelihood to access treatment), enabling resources (practical resources that impact ability to access treatment), and need (how perception of health motivates a person to access treatment).[114,115] Our goal is to comprehensively assess how these different factors influence treatment uptake and what barriers persist among subgroups of PWID. Aim 1 will look at how treatment penetration in the community, varies across Baltimore neighborhoods where ALIVE participants reside and how neighborhoods with low treatment penetration vary by neighborhood characteristics and composition of individuals with respect to predisposing factors. In Aim 2, we will evaluate how a critical enabling resource "HCV knowledge" differs by predisposing factors and enabling resources. Finally, Aim 3 will look at changes in HCV treatment initiation based on predisposing factors, enabling resources, and need.

Figure 1. Conceptual Framework



Summary

Given the changes in the HCV treatment landscape, both modalities and accessibility, studies are needed to assess progress among PWID towards reaching the HCV incidence goal and identify groups that may not be accessing treatment today. The purpose of this thesis is to evaluate how treatment uptake among PWID has changed in Baltimore, Maryland. This compliments earlier work investigating barriers to HCV treatment during the interferon-era that was also conducted in the ALIVE study. The results can be used to inform programs and future research aimed at improving treatment uptake among PWID and support microelimination efforts in Baltimore, MD or other similar jurisdictions.

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Chapter 2. Geographic variation of HCV treatment penetration and associated characteristics in the interferon and direct acting antiviral eras among people who inject drugs (PWID) in Baltimore, Maryland

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ABSTRACT

Background: With the continued increase in hepatitis C virus (HCV) incidence among people who inject drugs (PWID), studies are needed to understand potential barriers to HCV treatment. Geospatial analyses are a way to not only identify geographic areas of poor treatment uptake but also evaluate the extent to which characteristics of the neighborhoods or individuals explain the observed trends.

Methods: Using serial cross-sectional data from the ALIVE study, which is a community-based cohort of current and former PWID in Baltimore, MD, we performed a cluster detection analysis to identify hotspots of higher than expected rates of HCV viremia, which we used as an indicator for HCV treatment need. We did this over the following time-periods, 2006-2007 (N=953), 2015-2016 (N=787), and 2017-2018 (N=528), meant to capture treatment penetration prior to direct acting antivirals, early in the availability of direct acting antivirals, and current assessment, respectively. Additionally, we performed a multilevel regression analysis to understand the environmental and individual-level factors that explained the clustering.

Results: In the 2006-2007 time-period, the median proportion of viremic participants in Census tracts was 83%. We identified a single cluster, located in Central Baltimore City, that was in areas where the prevalence of HCV viremia was >91% and in areas of highest neighborhood deprivation (aOR: 6.55, 95% CI: 4.27, 10.05). The median proportion of viremic participants per Census tract decreased to 64% in the 2015-2016 time-period. Additionally, we identified two clusters in East and West Baltimore City. The odds of being in either of the clusters were higher among participants who are Black (aOR: 2.53, 95% CI: 1.41, 4.56) and increased with neighborhood deprivation. In the 2017-2018 time-period, the

median proportion of viremic participants per Census tract was 39% and we failed to identify any clusters of poor treatment penetration.

Conclusion: We found that HCV treatment penetration improved throughout Baltimore City and Baltimore County between the interferon and direct acting antiviral (DAA) eras. While it appears that by the late DAA-era (2017-2018) that treatment had penetrated all parts of Baltimore, MD, treatment uptake was slower in areas of higher neighborhood deprivation.

INTRODUCTION

Hepatitis C virus (HCV) is the most common bloodborne infection in the US, with 2.4 million people chronically infected.[1] Injection drug use (IDU) continues to be the most common risk factor, and HCV prevalence among people who inject drugs (PWID) ranges between 50%-90%.[2–5] In the US, the reported number of cases of acute HCV infection was decreasing in 1992 and stabilized around 2004. However, between 2010 and 2018 the reported number of cases increased 4.1-fold.[6–8] This increase was driven primarily by high incidence among young PWID who were increasingly white, female and living outside of urban settings, consistent with the shifting epidemiology of injection drug use across the US.[9–11] By contrast, HCV-related mortality is highest among individuals born between 1945-1965, who were infected in the 1990s, when HCV incidence peaked in the US.[7,12]

Of those infected with HCV, roughly 25% will spontaneously clear the virus.[13] Therefore, confirmatory HCV RNA testing is required to determine HCV chronicity. The 75% who do not spontaneously clear the virus will have a detectable HCV RNA viral load, indicating chronic HCV infection and a need for HCV treatment. Prior to 2013, HCV treatment lasted up to 48 weeks, included weekly interferon injections, adverse side effects, and cure rates of <50%.[13–15] Today, treatment requires one pill taken daily for as few as 8-weeks, and cure rates of >95%.[16–20] Because of the high burden of HCV, the increasing occurrence of liver-related morbidity and mortality secondary to HCV and advancements in treatment, in 2015, the World Health Organization and National Academies of Science, Engineering, and Medicine have set a goal to eliminate HCV by 2030 by specifically, lowering HCV incidence by 90% and HCV-related mortality by 65%.[21,22]

To meet these goals, countries around the world have made efforts to increase both HCV screening and linkage to treatment. However, limited progress has been made. Modelling done by the Polaris Observatory found that of 45 high-income countries, only nine were on

track to eliminate HCV by 2030 and an additional six by 2050.[23] While the United States is projected to achieve the HCV-mortality goal of 65% reduction by 2023, it is not on track to meet the HCV incidence goal.[23] In particular, in order to reduce HCV incidence, efforts will need to focus on treating all infected persons with hepatitis C particularly those groups that are driving ongoing transmission, such as PWID. But resources are limited and PWID experience a combination of individual, provider and structural barriers to HCV treatment.[24–27] In fact, it is estimated that only 16% of PWID were treated with DAAs between 2015 and 2017.[28,29]

To address this discrepancy, innovative strategies to identify and engage PWID in HCV treatment are needed. Use of geographic information system (GIS) and spatial statistical methods have been widely used to improve screening programs, allocate resources, and even identify key populations at risk.[30–33] In particular, cluster detection can be used to identify areas where the observed rates of disease are higher than what would be expected. Indeed, research using cluster detection approaches has helped to identify and characterize hotspots of HCV infection and HCV-related morbidity and mortality.[27,34,35] Similarly, this type of analysis can be used to identify areas with lower than expected penetration of HCV treatment. Further understanding of individual and structural factors that differentiate the observed clusters of infection and/or low treatment penetration and how these change over time can be used to better understand gaps in service delivery and highlight where to target resources or interventions.

The aim of this paper is to examine changes in the spatial distribution and clusters of HCV treatment need among PWID in Baltimore City and Baltimore County, Maryland, over three time-periods: 2006-2007 (pre-DAA era), 2015-2016 (early years of DAA availability), and 2017-2018 (later years of DAA availability). Furthermore, we examined whether any neighborhood and individual-level factors explained the observed clustering.

METHODS

Study Population

The AIDS Linked to the IntraVenous Experience (ALIVE) study is a community-based cohort of current and former PWID that has been described elsewhere.[36] In total, 5,358 individuals have been enrolled in ALIVE over five time periods: 1988-1989 (N=2,946), 1994-1995 (N=434), 1997-1998 (N=295), 2005-2008 (N=1,009), and 2015-2018 (N=674). All participants are ≥18 years of age and had a history of injection drug use (IDU) at enrollment. For the purposes of this analysis, we included all HCV-antibody positive participants who reported living in either Baltimore City or Baltimore County and received confirmatory HCV RNA testing. Additionally, each included participant had at least one clinic visit in one of three time periods: 2006-2007 (N=953), 2015-2016 (N=787), and 2017-2018 (N=528). A positive HCV RNA test indicated the participant had chronic HCV infection and was eligible for treatment; whereas a negative HCV RNA test was defined as either spontaneous clearance or successful treatment in the past. The time periods were selected to examine the period prior to the availability of direct acting antivirals (2006-2007), early in the availability of direct acting antivirals when multiple restrictions reduced access to HCV treatment (2015-2016), and a current assessment of HCV treatment need, 4-years since the availability of direct acting antiviral agents (2017-2018).[13,37–40]

Data Measurement

At baseline, participants provided information regarding sociodemographic characteristics (i.e. age, sex, race, education level). At semi-annual visits, participants were asked whether they were incarcerated for at least 7-days, recent drug use, used syringe service program, and health-related variables (i.e. type of insurance, whether a participant has a primary care provider, and whether a participant had an outpatient or emergency department visit)

through standardized questionnaires that were administered by either a trained interviewer or audio computer-assisted self-interview (ACASI). Variables collected at the semi-annual visits reflect usage in previous 6-months. All participants were screened for HCV antibodies at their baseline visit using an enzyme-linked immunosorbent assay (ELISA) (Ortho Clinical Diagnostics, Raritan, NJ) and received confirmatory testing using an HCV RNA test (Abbott Molecular, Des Plaines, Ill). HCV RNA testing was conducted annually with additional testing to confirm cure among participants who self-reported initiating HCV treatment between visits. Participants were screened for HIV at each study visit using an ELISA and Geenius HIV 1/2 Confirmatory Assay (Bio-Rad, Hercules, California). An HIV RNA test was performed on HIV-positive participants at each visit to determine HIV viral suppression (≤50 copies/ml). A FibroScan, which is an ultrasound that measures liver stiffness (i.e. fibrosis), was also performed. At each visit, participants provided an updated residential address that was geocoded and mapped using ArcGIS 10.7 (ESRI, Redlands, California) to 2010 US Census tracts. For participants with more than one visit in a study period, we included the address and responses reported at the first visit.

For the analysis, we evaluated individual-level variables that had been previously associated with treatment uptake, including demographics (i.e. age, sex, race, education level), whether a participant was incarcerated for at least 7-days, HIV status and HIV viral load, type of health insurance, recent engagement in medical care (i.e. having regular source of primary care, outpatient visit, visit to emergency department), use of harm reduction services (i.e. visit to syringe service programs) and type of drug use.[37,41–43] All variables, except demographic characteristics reflect use in the previous 6-months. We categorized type of drug use, based on if the participant reported no recent drug use, injection drug use only (i.e. injection of heroin, methamphetamine, cocaine, or speedball), non-injection drug use only (i.e. smoking crack or heroin), or both injection and non-injection drug use.

In addition to individual level characteristics, we examined neighborhood-level factors impacted treatment need. Specifically, we evaluated neighborhood deprivation, as it has been previously associated with increased treatment need in other studies.[34,44] To measure neighborhood deprivation, we created a neighborhood deprivation score for the 200 Census tracts that make up Baltimore City and 214 that make up Baltimore County using variables obtained from the 2011-2015, 5-year estimate from the American Community Survey .[45] Scores were calculated from a scale that was created using a principle component analysis with the following seven indicators that had been validated in Baltimore, Maryland and used in prior studies among ALIVE participants: percent of individuals in professional/managerial occupations, percent of households receiving public assistance, percent of households with crowding, percent of households living below the federal poverty level, percent female headed households living with dependent children (<18 years of age), percent of individuals with high school education or less, and percent of males and females (>16 years) that were unemployed.[45–47] The principle component analysis was performed on all 414 Census tracts, but our analysis only includes those with at least one ALIVE participant. In total, there were 209 Census tracts included for the 2006-2007 time-period, of which 157 (75.1%) were in Baltimore City, 211 Census tracts included for the 2015-2016 time-period, of which 162 (76.8%) were in Baltimore City, and 179 Census tracts included for the 2017-2018 time-period, of which 147 (82.1%) were in Baltimore City.

Statistical Analysis

We first compared the sociodemographic and behavioral characteristics of participants who were HCV RNA positive (indicating treatment need) and those who were HCV RNA negative using a chi-squared or Fisher's exact test for categorical variables, and a Wilcoxon-Mann-Whitney test for continuous variables. Because the proportions in Census tracts with a small number of ALIVE participants can be unstable or extreme, we mapped the spatial

distribution of HCV treatment need pre- and post-availability of DAAs by using Empirical Bayes Smoothing to calculate the smoothed proportion of ALIVE participants with chronic HCV infection throughout Baltimore City and Baltimore County using GeoDa 1.14.0.[48,49] This technique uses study data to estimate parameters, which are a weighted average of the raw data and a global average. The magnitude of the weight is proportionate to the population at-risk.[50] As such, proportions from Census tracts with a small number of ALIVE participants will be weighted more than Census tracts with larger numbers of ALIVE participants.[49] The results were exported from GeoDa and visualized using ArcGIS for the three time periods (2006-2007, 2015-2016, and 2017-2018). Results ranged from 0, indicating none, and 1, indicating all ALIVE participants in that Census tract required HCV treatment.

We identified statistically significant clusters of greater than expected treatment need based on the ratio of ALIVE participants with chronic HCV infection in each potential cluster using SaTScan Version 9.4.4, a cluster detection software.[51] SaTScan uses a circular moving window method to compare the number of observations in the study data with the expected number observations, determined using indirect standardization, within each potential candidate cluster. The potential clusters are evaluated using a likelihood ratio test, which are compared to 999 simulated likelihood ratios using Monte Carlo simulations. Finally, a p-value is assigned to identify the most likely clusters, removing those that were likely to appear due to chance.[51,52] The maximum cluster size was set to 25% of the population at-risk and required at least 4 cases to be considered a cluster. Clusters presented in the results had a p-value<0.05.

Initially, we performed a purely spatial cluster detection that used a Bernoulli model, where individual participant locations are treated as cases (i.e. those who were HCV RNA positive), or controls (i.e. those who were HCV RNA negative), and used a maximum likelihood ratio test to identify scanning windows with an elevated likelihood of HCV viremia. For each

potential cluster, the null hypothesis is complete spatial randomness of cases and controls, where the ratio of participants with a detectable HCV RNA test in the potential cluster is equal to the ratio outside of the cluster. Additionally, we restricted the analysis to include all data from 2015 through 2018 to perform a Bernoulli space-time cluster detection (since annual data were only available from this time-period). This approach is like the purely spatial scan statistic, except data are treated longitudinally. This allows for the identification of clusters over different durations of time. In a space-time scan statistic, a cylinder, rather than circular window, is used to identify clusters. The height is based on the duration that the cluster is present. Results from both scan statistics were imported into ArcGIS to visualize the detected clusters.

A subsequent analysis adjusted for participant characteristics and neighborhood deprivation of each Census tract to examine the degree to which clusters were explained by individual and neighborhood-level factors. The same variables were included for the three time periods for comparability and chosen based on *a priori* knowledge, as they had been shown to be independently associated with HCV treatment uptake in other studies. Multilevel logistic regression was performed using Stata 14 (StataCorp, College Station, Texas) to calculate the predicted probability of a participant having chronic HCV infection. Since the predicted probabilities are treated as a continuous variable, they were analyzed using the Gaussian (i.e. normal) model when imported back into SaTScan. This adjusted analysis identified clusters that were not explained by the regression covariates. The process was repeated for each of the three time-points to evaluate how clusters of poor treatment uptake changed over time.

Finally, we used multilevel logistic regression to identify factors independently associated with the clusters of HCV treatment need. Specifically, we compared persons who reported residence inside vs. outside an identified significant cluster as the dependent variable in a

model. For continuity, variables included in the final model were the same as those used in the adjusted cluster detection. This analysis was also performed using Stata 14 (StataCorp, College Station, Texas).

RESULTS

Baseline Characteristics

Baseline characteristics of the study participants are presented in Table 1. Among the 953 HCV-antibody positive participants in the 2006-2007 time period, 798 (84%) had chronic HCV infection, the median age was 48 years, 68% were male, 85% were Black, 26% were insured through Medical Assistance, and 56% reported injecting drugs in the previous 6-months. In 2015-2016, 64% of the 787 participants had chronic HCV infection, the median age was 56 years, percentage that were male was 78%, 88% were Black, 53% had Medical Assistance, and 27% reported recent injection drug use. Finally, prevalence of chronic HCV was 57% among the 528 HCV-antibody positive participants with a visit in the 2017-2018 time period, the median age was 57 years, 67% were male, 91% were Black, 48% had Medicaid Assistance, and 32% injected drugs in the last 6 months.

Spatial Analysis Results

Figure 1 shows that the proportion of HCV-antibody positive participants requiring HCV treatment per Census tract decreased over the three study periods. The median percentage of participants with HCV viremia in Baltimore City and Baltimore County fell from 83% in the interferon-era, to 64% in the early DAA-era, and finally 39% in the later DAA-era. In Baltimore City, the percentage of Census tracts in which ≥74% of the participants had HCV viremia dropped from 89% in the interferon-era to 20% in the early DAA-era and 2% in the later DAA-era.

Purely Spatial Cluster Detection

Results from the purely spatial cluster detection identified a single cluster of higher than expected HCV treatment need located in Central Baltimore City in the interferon-era (Figure 2a). The cluster was located in an area where the proportion of HCV viremic ALIVE participants exceeded 0.91. No clusters were identified using a purely spatial cluster detection for the two later time-periods. We performed an adjusted cluster detection using a normal model for all three time-periods but failed to identify any significant clusters ($p>0.05$). Participant and neighborhood-level characteristics of the identified clusters in the interferon-era (2006-2007) are presented in Table 2. While being Black was associated with a 68% (95% CI: 1.02, 2.74) increase in the odds of being in a cluster in the univariable analysis for the 2006-2007 time-period, it failed to retain statistical significance after adjusting for other sociodemographic characteristics, healthcare utilization, recent drug use, and neighborhood socioeconomic status. Neighborhood deprivation was significantly associated with being in a cluster in univariable and multivariable analysis. Clusters had more than 6 times the odds (95% CI: 4.09, 9.93) of being in a highly deprived Census tract compared to not being in a cluster in the adjusted model.

Space-Time Cluster Detection

We identified two clusters in the early DAA-era (2015-2016) using the space-time cluster detection for 2015-2018 (Figure 2b). The location of the clusters coincides with where the proportion of HCV-antibody positive participants with detectable HCV viremia was highest in East and West Baltimore City. Subsequently, we performed an adjusted cluster detection using a normal model. We failed to identify any significant clusters ($p>0.05$) after controlling for sociodemographic characteristics, recent drug use, and healthcare utilization. The participant and neighborhood-level characteristics describing the two identified clusters in the early DAA-era are presented in Table 2. The odds of being in a cluster were higher if a

participant was older (OR: 1.02; 95% CI: 1.00, 1.04), if a participant was Black (OR: 3.01; 95% CI: 1.78, 5.10), , and in the most deprived Census tracts. In the adjusted model, all levels of neighborhood deprivation and Black race (aOR: 2.53; 95% CI: 1.41, 4.56) continued to be significantly associated with higher odds of being in a cluster, although the associations were attenuated.

DISCUSSION

Our study found that there was significant penetration of HCV treatment in Baltimore City and Baltimore County. There was a 23% decrease in the median proportion of viremic participants between the interferon-era and the early DAA-era and a 39% decrease between the early and later DAA time-periods. Results from the cluster detection analysis identified clusters in both the pre-DAA and early DAA eras, which reflect, in part, where infections were located, as well as areas where access or prioritization of healthcare may have been impeded by poverty. It was encouraging that we did not identify clusters in the later DAA-era, which could indicate that HCV treatment among PWID has penetrated throughout Baltimore and may even be reaching the most vulnerable.

Clusters of poor treatment uptake that were identified in the interferon-era and early in the DAA-era, highlight health inequities resulting from poverty. In the interferon-era, many providers and patients chose to defer treatment until DAAs became available.[53,54] Since treatment uptake was so low, the cluster of HCV viremia likely represented where HCV infection was located. Starting in 2014, treatment uptake improved initially. However, the two early DAA-era clusters detected in East and West Baltimore City show that it was not uniform across the city. While we did not identify many factors that differentiated clusters of elevated HCV treatment need, in both periods, neighborhood deprivation and race was

associated with a significantly higher likelihood of being in a cluster. In both the interferon and early DAA-era, HCV treatment initiation has been shown to differ by race, with Black individuals being less likely to start HCV treatment than their white counterparts.[55–57] So it was not surprising that Black race was associated with being in a cluster of HCV treatment need. Moreover, poverty is known to be associated with negative health outcomes, often due to poor healthcare accessibility. The identified clusters were located in Central, East and West Baltimore, which are areas with high levels of neighborhood deprivation, but they are also home to major health systems where PWID can receive HCV treatment. Further research is needed to elucidate if the treatment delay was related to poor access to HCV care or provider and individual-level barriers affecting treatment initiation, like stigma or competing priorities.

Remarkably, in failing to identify any clusters in the later DAA time-period, we found that HCV treatment had penetrated the PWID community, and in a more equitable manner. It is likely a result of a mixture of factors that occurred over the 4-years since DAAs became available. For example, efforts were made to expand HCV treatment into primary care, which increased the number of providers that treat HCV, and awareness of DAAs improved the longer they were available.[58] Additionally, changes in Maryland's Medicaid restrictions may also explain why treatment uptake among ALIVE participants continued to improve throughout the DAA-era. Early in their implementation, participants able to circumvent the restrictions were older, had cirrhosis, and had not injected drugs in some time. However, we found that the percentage of chronically infected participants with cirrhosis and who had no recent drug use decreased between the early and late DAA-eras, despite the percentage of participants with Medicaid staying roughly the same.[58] This is encouraging, as it shows that treatment had expanded to groups of PWID who were initially precluded from DAA-based therapies.

Even though treatment uptake improved over the study period, 43% of those with visits in the late DAA-era were in need of treatment. These groups may be the most challenging to reach, suggesting that increased efforts will be needed to ensure these PWID initiate treatment. Our results showed that the median percentage of viremic participants fell to 39% in the late DAA-era, but was over 63% in areas in East and West Baltimore and 91% in Southwest Baltimore, MD. Further research is needed to understand the individual barriers these PWID are experiencing. But public health officials could use our results to place support that is aimed to improve access to treatment in these locations.

Our study is not without limitations. First, we did not include whether a person self-reported treatment at a visit and so, the presence/absence of viremia reflects a combination of treatment and spontaneous clearance. Results from the interferon-era most likely reflect spontaneous clearance of HCV since so few participants were treated. The mere reduction in HCV viremia in the latter two time periods reflects at least some contribution of treatment; in the absence of treatment uptake, that proportion would be expected to remain stable.[53] While ALIVE is a longitudinal cohort, the analyses looked at serial cross-sections given that HCV viremia data were not available for every participant at every visit. While HCV and HIV status were laboratory confirmed in our study, other variables, like drug use and healthcare utilization, are based on self-report and are subject to recall bias. An earlier study in ALIVE evaluated social desirability responding in discussing recent drug use and found high reliability and validity.[59,60] Finally, since participants volunteer to be in the ALIVE study, participants may not be representative of the larger population of PWID in Baltimore or in other geographic areas. However, the demographic characteristics between cohorts suggest that the ALIVE study remains representative of the underlying population of PWID.

To decrease HCV incidence by 90%, efforts must be made to improve treatment uptake among PWID. Geospatial analyses could help inform interventions aimed to identify areas

which would benefit most from additional resources to improve linkage to treatment and monitor the effect overtime. Our study successfully used geospatial and statistical analysis to identify and explain changes in areas of poor HCV treatment penetration among ALIVE participants living in Baltimore City and Baltimore County in three time periods. Results can be used by public health officials to continue to monitor HCV treatment need and intervene in hotspots, as they occur.

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Table 1. Individual and neighborhood characteristics of HCV-antibody ALIVE participants by HCV RNA status, Baltimore City and Baltimore County, 2006-2018

HCV Status	2006-2007			2015-2016			2017-2018		
	Antibody Positive Only	Chronic Infection	p-value	Antibody Positive Only	Chronic Infection	p-value	Antibody Positive Only	Chronic Infection	p-value
N	155	798		286	501		302	226	
Demographic Characteristics									
Age (years), mean (IQR)	45.3 (8.5)	47.7 (8.0)	<0.01	57.3 (7.8)	55.1 (8.1)	<0.01	57.5 (6.9)	54.6 (8.0)	<0.01
Black race	119 (76.8%)	695 (87.1%)	<0.01	250 (87.4%)	443 (88.4%)	0.67	279 (92.4%)	201 (88.9%)	0.17
Female sex	70 (45.2%)	235 (29.4%)	<0.01	97 (33.9%)	156 (31.1%)	0.42	100 (33.1%)	75 (33.2%)	0.99
≥High school diploma	65 (41.9%)	313 (39.3%)	0.54	130 (45.5%)	199 (39.9%)	0.13	136 (45.0%)	92 (40.9%)	0.34
Incarcerated for at least 7 days	23 (14.8%)	141 (17.9%)	0.36	9 (3.2%)	18 (3.6%)	0.75	5 (1.7%)	9 (4.0%)	0.10
Comorbidities and Healthcare Utilization									
Estimate of fibrosis (liver scarring)									
Mild liver scarring	59 (38.1%)	190 (23.9%)		78 (27.4%)	128 (25.6%)		78 (25.9%)	44 (19.5%)	
Significant liver scarring	8 (5.2%)	98 (12.3%)	<0.01	23 (8.1%)	62 (12.4%)	<0.01	40 (13.3%)	52 (23.0%)	0.02
Severe scarring	5 (3.2%)	46 (5.8%)		9 (3.2%)	40 (8.0%)		27 (9.0%)	21 (9.3%)	
Cirrhosis	83 (53.5%)	462 (58.0%)		175 (61.4%)	270 (54.0%)		156 (51.8%)	109 (48.2%)	
HIV status and HIV viral suppression[1]	38 (24.5%)	234 (29.3%)		116 (40.6%)	163 (32.5%)		183 (60.6%)	100 (44.2%)	
HIV negative	117 (75.5%)	564 (70.7%)		170 (59.4%)	338 (67.5%)		119 (39.4%)	126 (55.8%)	
HIV-positive with undetectable viral load	10 (6.5%)	90 (11.3%)	0.19	109 (38.1%)	110 (22.0%)	<0.01	144 (47.7%)	55 (24.3%)	<0.01
HIV-positive with detectable viral load	28 (18.1%)	144 (18.1%)		7 (2.5%)	53 (10.6%)		39 (12.9%)	45 (19.9%)	
Insurance status[2]									
No insurance	70 (45.2%)	331 (41.6%)		8 (2.8%)	10 (2.0%)		5 (1.7%)	2 (0.9%)	
Insurance through Medical Assistance	40 (25.8%)	213 (26.8%)	0.83	133 (46.5%)	282 (56.5%)	0.03	122 (40.5%)	131 (58.5%)	<0.01
Other type of insurance	45 (29.0%)	251 (31.6%)		145 (50.7%)	207 (41.5%)		174 (57.8%)	91 (40.6%)	
Had a primary care provider[2]	109 (70.3%)	573 (71.8%)	0.71	264 (92.3%)	445 (88.8%)	0.12	285 (94.4%)	197 (87.2%)	<0.01
Had outpatient visit[2]	80 (51.6%)	423 (53.0%)	0.75	242 (84.6%)	371 (74.1%)	<0.01	267 (88.4%)	167 (73.9%)	<0.01
Visited emergency department[2]	44 (28.4%)	255 (32.0%)	0.38	86 (30.1%)	150 (29.9%)	0.97	77 (25.7%)	78 (34.7%)	0.03
Drug Use Practices									
Type of drug use[2]									
None	52 (33.5%)	294 (36.9%)		202 (70.6%)	273 (54.7%)		183 (60.6%)	93 (41.3%)	
Injection drug use only	30 (19.4%)	170 (21.3%)	0.56	21 (7.3%)	61 (12.2%)	<0.01	29 (9.6%)	34 (15.1%)	<0.01
Non-injection drug use only[4]	16 (10.3%)	61 (7.7%)		29 (10.1%)	72 (14.4%)		41 (13.6%)	40 (17.8%)	
Both	57 (36.8%)	272 (34.1%)		34 (11.9%)	93 (18.6%)		49 (16.2%)	58 (25.8%)	
Visited the syringe service program[2]	25 (16.2%)	110 (13.8%)	0.43	22 (7.7%)	73 (14.6%)	<0.01	29 (9.6%)	51 (22.7%)	<0.01
Neighborhood Characteristics									
Neighborhood deprivation score									
Quartile 1 (lowest level of deprivation)	41 (26.5%)	203 (25.4%)		88 (30.8%)	112 (22.4%)		78 (25.8%)	54 (23.9%)	
Quartile 2	34 (21.9%)	205 (25.7%)	0.26	61 (21.3%)	134 (26.7%)	<0.01	83 (27.5%)	52 (23.0%)	0.36
Quartile 3	49 (31.6%)	198 (24.8%)		58 (20.3%)	142 (28.3%)		68 (22.5%)	65 (28.8%)	
Quartile 4 (highest level of deprivation)	31 (20.0%)	192 (24.1%)		79 (27.6%)	113 (22.6%)		73 (24.2%)	55 (24.3%)	

[1]Viral suppression is defined as ≤50 copies per mL

[2]Reflective of last 6 months

[3]Includes injection of heroin, cocaine, speedball (heroin and cocaine together), methamphetamine or any other type of drug

[4]Includes smoking crack or heroin

Table 2. Participant and neighborhood-level correlates of membership in a cluster of elevated HCV treatment need among ALIVE participants, Baltimore City and Baltimore County, 2006-2007 and 2015-2016

	Characteristics of 2006-2007 unadjusted purely spatial cluster		Characteristics of 2015-2016 unadjusted space-time clusters	
	OR (95% Conf. Interval)	aOR (95% Conf. Interval)	OR (95% Conf. Interval)	aOR (95% Conf. Interval)
Age (years)	1.01 (0.99, 1.03)	1.00 (0.97, 1.02)	1.02 (1.00, 1.04)	1.00 (0.98, 1.03)
Participant's race				
Non-Black	REF	REF	REF	REF
Black	1.68 (1.02, 2.74)	1.24 (0.67, 2.28)	3.01 (1.78, 5.10)	2.53 (1.41, 4.56)
Participant's sex				
Male	REF	REF	REF	REF
Female	1.13 (0.82, 1.57)	1.00 (0.67, 1.49)	1.29 (0.95, 1.74)	1.20 (0.87, 1.67)
HIV status and HIV viral suppression[1]				
HIV negative	REF	REF	REF	REF
HIV-positive with undetectable viral load	0.90 (0.53, 1.52)	0.94 (0.51, 1.73)	1.11 (0.80, 1.53)	1.09 (0.77, 1.54)
HIV-positive with detectable viral load	1.09 (0.73, 1.62)	1.23 (0.77, 1.96)	1.17 (0.68, 2.01)	1.04 (0.59, 1.83)
Had outpatient visit[2]				
No	REF	REF	REF	REF
Yes	0.83 (0.61, 1.12)	0.82 (0.57, 1.18)	1.15 (0.81, 1.63)	1.11 (0.76, 1.61)
Type of drug use[2]				
None	REF	REF	REF	REF
Injection drug use only[3]	1.01 (0.66, 1.55)	0.90 (0.54, 1.49)	1.19 (0.74, 1.92)	1.32 (0.80, 2.18)
Non-injection drug use only[4]	1.25 (0.70, 2.23)	0.90 (0.46, 1.75)	1.23 (0.80, 1.89)	1.29 (0.82, 2.03)
Both	1.12 (0.78, 1.62)	1.03 (0.66, 1.60)	0.96 (0.64, 1.43)	1.03 (0.67, 1.58)
Neighborhood deprivation score				
Quartile 1 (lowest level of deprivation)	REF	REF	REF	REF
Quartile 2	0.55 (0.32, 0.95)	0.53 (0.31, 0.92)	2.66 (1.72, 4.12)	2.53 (1.63, 3.94)
Quartile 3	0.34 (0.19, 0.63)	0.34 (0.18, 0.62)	3.31 (2.15, 5.10)	3.01 (1.93, 4.69)
Quartile 4 (highest level of deprivation)	6.55 (4.27, 10.05)	6.37 (4.09, 9.93)	3.10 (2.01, 4.80)	2.89 (1.85, 4.52)

[1]Viral suppression is defined as ≤50 copies per mL

[2]Reflective of last 6 months

[3]Includes injection of heroin, cocaine, speedball (heroin and cocaine together), methamphetamine or any other type of drug

[4]Includes smoking crack or heroin

Supplemental Table 1. Characteristics of purely spatial and space-time cluster detection, Baltimore City, 2006-2007, 2015-2016

	Number of Observations	Number of Expected Observations	Likelihood Ratio Test	Relative Risk	p-value
Purely Spatial Cluster, 2006-20017	105	91	9.56	1.15	0.03
Space-Time Cluster 1, 2015-2016	68	46	13.04	1.51	<0.01
Space-Time Cluster 2, 2015-2016	112	85	11.75	1.38	<0.01

Figure 1. Spatial distribution of HCV treatment need by Census tract among ALIVE participants using Empirical Bayes Smoothing, Baltimore City and Baltimore County, 2006-2007, 2015-2016, 2017-2018

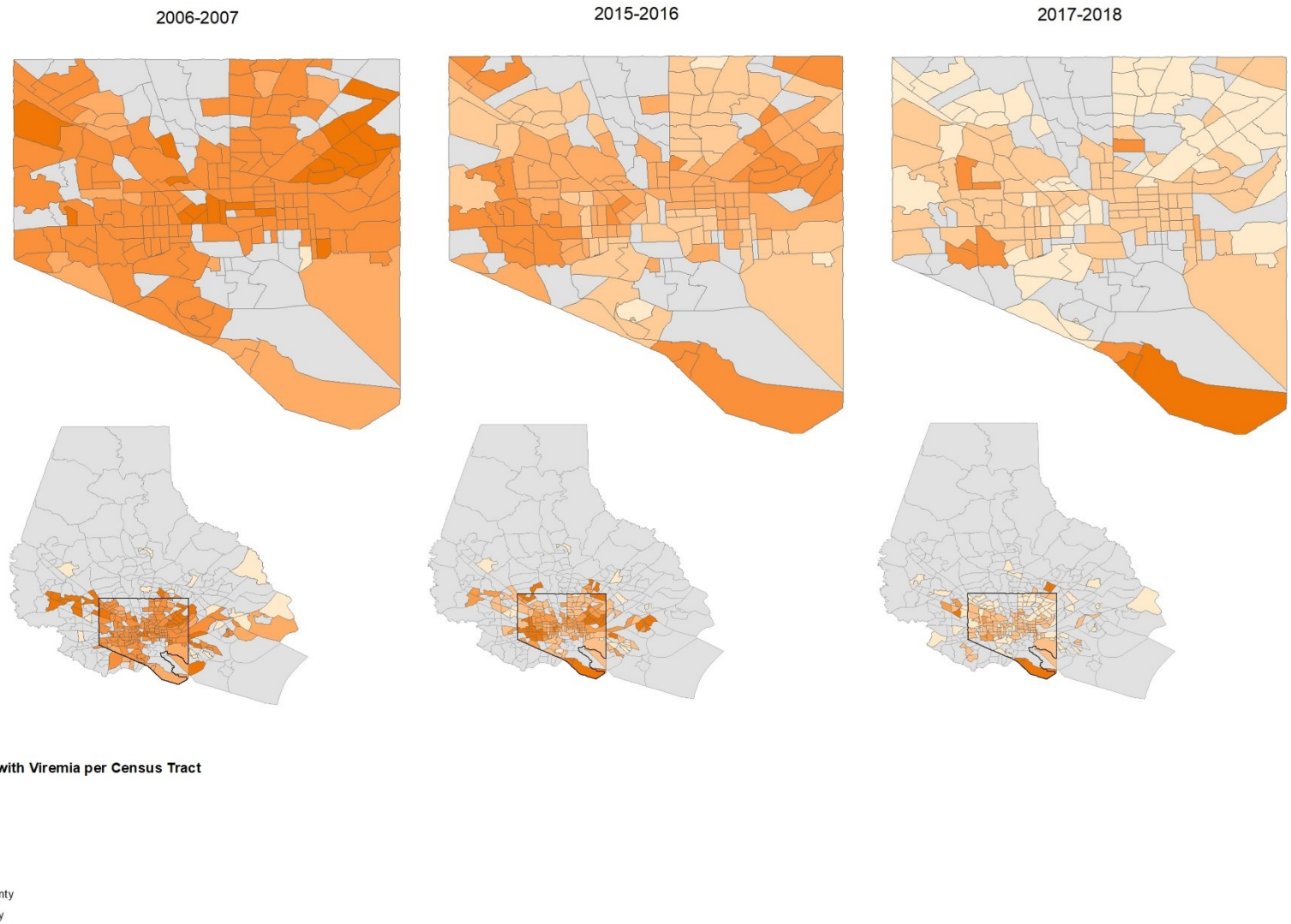
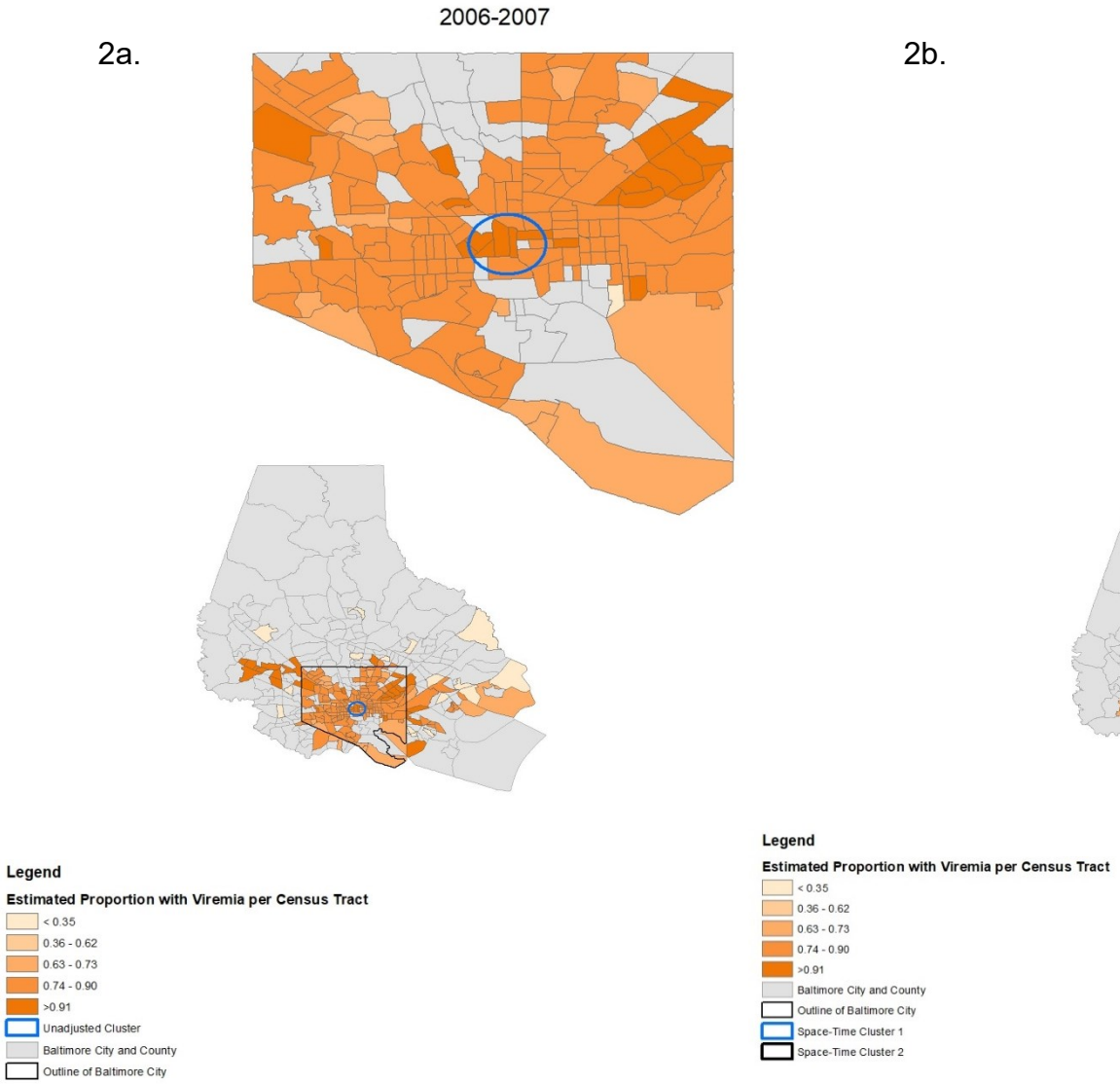
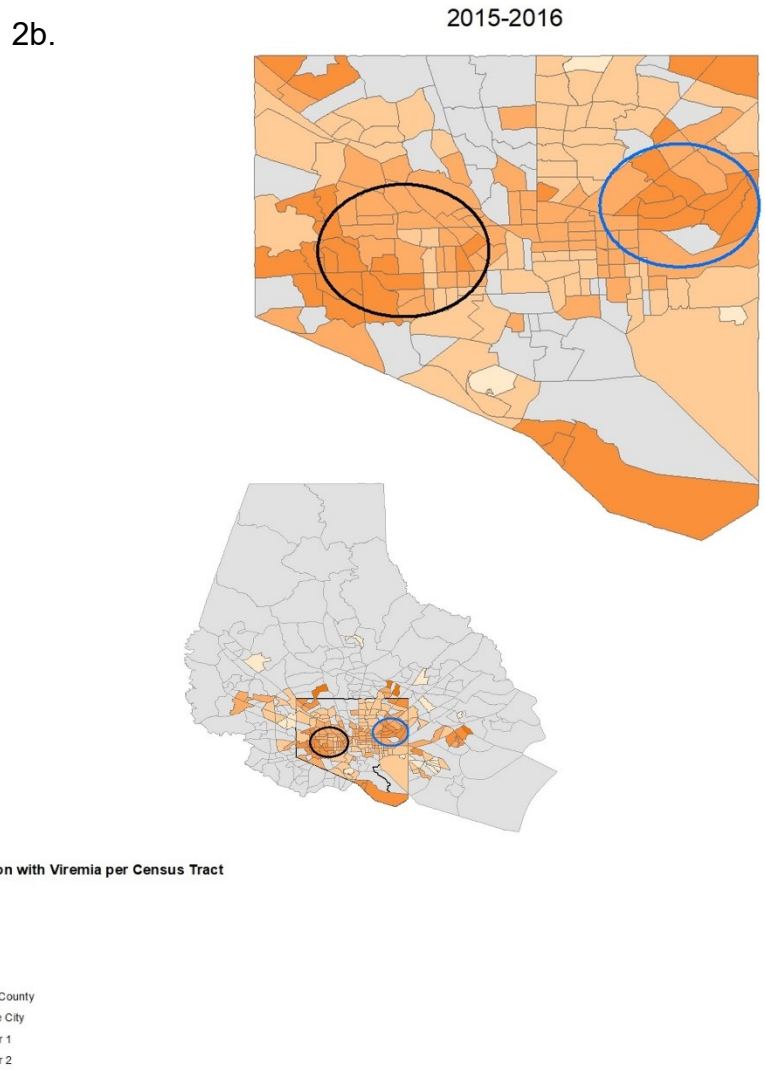


Figure 2a. Unadjusted purely spatial cluster of HCV treatment need in Baltimore City and Baltimore County, 2006-2007*
Figure 2b. Unadjusted space-time clusters of HCV treatment need in Baltimore City and Baltimore County, 2015-2016*





*The background choropleth map are the smoothed results from Figure 1.
Note: No statistically significant clusters were identified in the last time-period, 2017-2018 or in the adjusted analyses.

Chapter 3. Assessing knowledge of HCV and direct acting antivirals among people who inject drugs (PWID) by HIV and HCV status, in Baltimore, Maryland

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ABSTRACT

Background: Two commonly cited barriers to interferon-based treatment were low knowledge of HCV and fear of treatment-related side effects. With the availability of direct acting antivirals (DAA), interferon-based therapies are now obsolete, but treatment uptake remains low in subgroups of people who inject drugs (PWID). It is possible that knowledge of DAAs may motivate some to seek treatment but, the extent to which information about DAAs has penetrated PWID is not well-characterized.

Methods: Using results from a 17-item assessment of HCV knowledge, collected from 826 current and former PWID who were recruited into the ALIVE study between 2015-2018, we created three knowledge scores to measure awareness of HCV-related transmission (7-questions), HCV natural history (5-questions), and HCV treatment (3-questions) by HIV and HCV status. We used the highest quartile of responses as the cut-point for high/low knowledge on the transmission and natural history subscales. A participant was classified as having high treatment knowledge if they correctly answered the 3 treatment-related questions. Subsequently, we performed a logistic regression to identify subgroups of PWID who were at-risk of low HCV knowledge.

Results: Nearly all participants correctly answered which injection drug use related practices could result in HCV transmission and that HCV negatively affects a person's liver (95%) but is largely asymptomatic (97%). While 80% correctly answered that HCV was curable, only two-thirds correctly stated that HCV treatment now has fewer side effects, shorter duration, and decreased pill burden, compared to interferon-based therapies. Overall, 23% of the participants had a high transmission knowledge score and no independent predictors of having high transmission knowledge were identified. In the natural history subscale, 31% of the participants had a high knowledge score and high knowledge was associated with having a high school

diploma (aOR: 1.41, 95% CI: 1.02, 1.95), and having shared needles in the past. In total, 78% of the participants had high knowledge of HCV treatment. We found that high treatment knowledge was associated with being HCV mono-infected compared to HCV negative. Additionally, among those who were HCV positive, treatment knowledge was higher among those diagnosed with HCV prior to study entry, compared to those who were diagnosed through HCV testing at ALIVE.

Conclusion: HCV knowledge among this population of PWID was high. However, misinformation about interferon-based therapies remain. Treatment knowledge was lowest among participants who were HCV negative or unaware of their HCV infection, at the time of assessment, which suggests that HCV treatment is discussed at the time of testing or at some point afterwards.

INTRODUCTION

With 4.1 million people infected, hepatitis C virus (HCV) is the most prevalent bloodborne viral infection in the United States.[1,2] HCV is primarily transmitted through shared injection drug use (IDU) practices; in fact, prevalence of HCV among people who inject drugs (PWID) ranges between 50%-90%.[3–6] Between 2010 and 2018, there was a 4.1-fold increase in the reported number of cases of acute HCV infection in the US.[7,8] This corresponds with increased injection drug use among primarily younger, non-urban, white, and female individuals.[9,10] Furthermore, HIV/HCV coinfection is common and upwards of 90% of HIV-infected PWID are coinfected with HCV.[3,11] By comparison, the vast majority of HIV/HCV coinfected PWID in the US tend to be male, older than 50 years of age, and belong to ethnic minority groups reflective of the earlier heroin and cocaine epidemic in the 1980s and 1990s.[12,13]

However, HCV is curable and in late 2013, there was a remarkable shift in HCV treatment with the advent of direct acting antivirals (DAA).[14,15] Between 1991-2013, HCV treatment lasted up to 48 weeks, included weekly interferon injections, adverse side effects, and cure rates of <50%.[16–18] Today, treatment requires one pill taken daily for 8-12 weeks, minimal side effects, and cure rates of >95%.[19–23] In the US, it is projected that by 2030, 80% of all HCV infected individuals will be treated.[24] However, it is unlikely that access will be comparable across all populations. In particular, PWID face greater barriers to access than other groups and between 2015 and 2017, it was estimated that only 16% had been treated with DAAs.[25,26] In order to effectively improve treatment uptake among PWID , it will be important to identify barriers to HCV treatment in this new era of DAA-based treatment.

Barriers to HCV treatment are multifactorial and represent a confluence of individual, provider, and system barriers. These were well characterized in the interferon-era of treatment .[27,28] In particular, low knowledge of HCV and perceptions of treatment-related side effects were commonly cited reasons to explain poor initiation of HCV treatment among PWID.[27,29,30]

Furthermore, studies also found differential knowledge by HIV status.[29–32] In the DAA era, research has focused primarily on structural barriers given the restrictions placed on reimbursement of HCV treatment, particularly from Medicaid. In many settings, these structural barriers are dissipating, but less is known about the barriers that will remain.[33,34] In order to optimally reach all populations at risk for and infected with HCV, it is important to understand whether accurate information has penetrated within PWID communities, as it may be facilitator for testing or treatment initiation. Some DAA-era studies have found that major gaps in knowledge regarding HCV transmission and treatment remain.[35,36] However, these studies recruited participants from substance use treatment facilities, many of whom offer on-site HCV testing and counseling. As such, the results may not be representative of the broader PWID community. The aim of this study is to assess the extent to which knowledge of DAAs has penetrated the PWID community and assess whether subgroups that had low knowledge of interferon continue to have poor knowledge of DAAs. While the focus is on knowledge of DAA-based therapy, we also evaluated knowledge related to transmission and natural history of disease.

METHODS

Study Population

The AIDS Linked to the IntraVenous Experience (ALIVE) Study is a prospective community-based cohort of current and former PWID, located in Baltimore, Maryland, which has been described previously.[37] Participants were recruited independent of engagement in health or harm reduction services, through street outreach, flyer distribution, and peer referrals. To be eligible, individuals must have been ≥18 years of age and reported a history of injection drug

use (IDU). After the initial enrollment during 1988-1989, there have been additional enrollment periods in 1994-1995, 1998, 2000, 2005-2008, and 2015-2018.

This analysis includes persons who were enrolled into the ALIVE cohort from 2015-2018 (in the DAA-era). At their baseline visit, trained interviewers collected information on demographics, past drug use and medical history using standardized questionnaires. Participants were also screened for HIV using an enzyme-linked immunosorbent assay (ELISA) and Geenius HIV 1/2 Confirmatory Assay (Bio-Rad, Hercules, California) and HCV antibodies, using an ELISA (Ortho Clinical Diagnostics, Raritan, NJ). HIV positive participants further received an HIV RNA assessment (Roche, Basel, Switzerland) and HCV antibody positive participants received an HCV RNA test (Abbott Molecular, Des Plaines, Ill) to confirm active infection vs. clearance vs. cure. Participants who were HIV or HCV-positive upon entry were asked to self-report their engagement in specialty care, which included HCV treatment history. The enrollment process was completed with a second visit two to four weeks later where participants were asked about recent drug use, comorbidities, and healthcare utilization, reflective of the previous 6-months. In this study, the median time between the baseline and first follow-up visit was 33 days (IQR: 30-38). All participants were subsequently followed semi-annually.

Data Collection

A questionnaire on HCV knowledge was administered to all persons recruited from 2015-2018 at the baseline visit prior to the provision of counseling and testing related to HCV. The questionnaire was adapted from the HCV Follow-Up Questionnaire administered through NHANES and included 17 true/false questions to assess participant knowledge.[38] Specifically, the questions evaluate the participant's knowledge of HCV transmission (7-questions), natural history (5-questions), treatment (3-questions), clinical management (1-question), and prevention modalities (1-question). In this analysis we used the responses to questions regarding HCV transmission, natural history, and treatment, to generate a knowledge score for each subscale.

Additional variables of interest were classified based on laboratory testing and the surveys administered at the baseline and first follow-up visit. Those ascertained at the baseline visit, include demographic characteristics (i.e. age, sex, race, education level), lifetime needle sharing practices and participant's social network size (i.e. number of known PWID in Baltimore, MD, number of known HCV-positive PWID in Baltimore, MD). Those reported at the first follow-up visit included self-reported drug use (i.e. frequency of injection drug use, type of drug use), use of harm reduction services (i.e. syringe service programs and medication for opioid use disorder), and healthcare utilization (i.e. having source of primary care, outpatient visit, visit to emergency department). All characteristics ascertained at the first follow-up visit reflect use in the previous 6-months. Type of drug use was categorized as none, injection drug use only, non-injection drug use only, both injection and non-injection drug use. Injection drug use was defined as a participant's self-reported use of heroin, cocaine, speedball (heroin and cocaine) or methamphetamine through injection. Non-injection drug use was defined as use of heroin or crack use through inhalation. Finally, using ArcGIS, we calculated proximity from the participants' primary residence to the nearest substance use treatment facility, where PWID might receive information on HCV and HCV testing, which would be reflected in a higher knowledge score. These substance use facilities were identified through the Substance Abuse and Mental Health Services Administration (SAMHSA) Behavioral Health Treatment Services Locator. The list of facilities is updated annually using responses from SAMHSAs National Survey of Substance Abuse Treatment Services (N-SSATS) and National Mental Health Services Survey (N-MHSS). Additionally, new facilities that complete abbreviated versions of the surveys are added monthly.

Statistical Analysis

We used descriptive statistics to compare the sociodemographic and behavioral characteristics by participant HCV antibody and HIV status using a chi-square or Fisher's exact test for

categorical variables and a Wilcoxon-Mann-Whitney test for continuous variables. For knowledge regarding HCV transmission and natural history of HCV, we dichotomized HCV knowledge as either “high” or ‘low” using the highest quartile of the distribution of the number of questions answered correctly as the cut-point. Based on the distribution of correct responses, our cut-points indicating “high” knowledge related to HCV transmission and natural history were 86% and 80%, respectively. For HCV treatment knowledge, we classified “high knowledge” as correctly answering the three treatment-related questions correctly, and “low knowledge” as answering none, one or two of the knowledge questions correctly.

Separate univariable and multivariable logistic regression models were used to determine factors independently associated with high knowledge for each sub-scale. Initial models included all participants (N=826) recruited from 2015-2018 and only included covariates measured at the baseline visit. Of the 826 who attended the baseline visit, 637 (77%) also attended the first follow-up visit where information was collected on recent risk behaviors. Our second multivariable analysis also included information that was available for the 637 participants who returned for the first follow-up visit. Compared to those who did attend this visit, participants who did not were more likely to be HCV mono-infected, white, younger, and live outside of Baltimore City ($p<0.05$ for all). There were no statistically significant differences in HCV knowledge, lifetime drug use, social network size, or distance to substance use treatment facilities among those who did and did not attend the first follow-up visit. To pick our final models, we also considered all variables with a p-value ≤0.1 in the univariable analysis. If collinearity was detected between variables, we selected the one that was the most biologically/clinically meaningful. Variables in the final model were chosen based on an *a priori* hypothesis or because they had been shown to be associated with HCV knowledge in the literature. In both multivariable models, basic demographics, education level, proximity to services used by PWID, and the number of other PWID that the participant reported knowing

were included models, regardless of statistical significance, as they have been shown to be associated with HCV knowledge in prior literature. Variables measuring care (i.e. outpatient medical visits in the previous 6 months) or service utilization (i.e. prescription of medication for opioid use disorder) were retained in the final model because they represented potential opportunities for education about HCV that could result in higher knowledge scores. Variables were also retained in the final model if they were risk behaviors (i.e. frequency of injection drug use, recent injection drug use) that had been associated with low HCV knowledge in other studies.[31,39]

Because HCV knowledge is likely influenced by engagement in HIV and/or HCV care, additional analyses characterized persons by their HIV and HCV care status. First, among HIV/HCV coinfected participants, we evaluated differences in each of the knowledge types by whether persons had achieved HIV viral suppression. Similarly, among participants who were HCV antibody positive, we examined outcomes by three groups: (1) HCV infected, but not diagnosed; (2) HCV infected, diagnosed, but not treated; and (3) HCV infected, diagnosed and treated, upon entry to the study. All analysis was performed using Stata Version 14 (StataCorp, College Station, Texas).

RESULTS

Baseline Characteristics

Characteristics of the 826 participants who completed the HCV knowledge questions and 637 participants who returned for the first follow-up visit are presented in Table 1. Overall, the median age was 46 years, 71% were male, 54% were Black, 32% were HCV negative, 54% were HCV mono-infected and 14% were HIV/HCV coinfected. Among those who were HCV mono-infected and HIV/HCV coinfected, 64.3% and 59.6% reported having a previous positive

HCV test. Compared to those who were HCV negative, both HCV mono-infected and HIV/HCV coinfected participants were more likely to be older. HCV mono-infected were more likely to be white and HIV/HCV coinfected participants were more likely to be Black. Among participants who attended the first follow-up visit, HCV mono-infected participants were more likely to be prescribed medication for opioid use disorder, with little difference between HIV/HCV coinfected and HCV negative participants. Finally, healthcare utilization varied among the groups, where nearly all HIV/HCV coinfected participants had at least one outpatient visit, which was significantly higher than both HCV mono-infected and HCV negative participants.

HCV Knowledge Scale

Table 2 presents the individual items within the HCV knowledge scale, correct responses, and the percentage of participants who answered each question correctly by HIV and HCV status. In terms of injection-specific transmission knowledge, nearly all participants (99%) were aware that HCV is transmitted through sharing needles. While over 91% of both HCV mono-infected and HIV/HCV coinfected participants were aware that HCV could be transmitted by sharing works, like spoons or cookers, only 84% of HCV negative participants were aware. Responses to the natural history questions revealed that nearly all participants were aware that HCV can be asymptomatic (97%) and negatively affects your liver (95%), but participants were less familiar with the long-term health effects. However, we did see variability in responses between the three exposure groups regarding two of the treatment knowledge questions. Knowledge of HCV treatment was highest among HIV/HCV coinfected participants (77%), followed by HCV mono-infected participants (70%) and considerably lower among HCV negative participants (41%).

HCV Transmission Knowledge

Overall, 23% were classified as having high HCV transmission knowledge. In the univariable analysis, transmission-related knowledge did not differ significantly by HIV or HCV status (Table

3). However, transmission-related knowledge was significantly associated with younger age (OR: 1.02, 95% CI: 1.01, 1.04), a lifetime history of needle sharing (OR: 1.54, 95% CI: 1.01, 2.34), increased frequency of injection drug use, and among participants who were Black (OR: 0.68, 95% CI: 0.48, 0.94). However, no variables were associated (P>0.05) with transmission knowledge in either multivariable models.

HCV Natural History Knowledge

In total, 31% participants were classified as having a high knowledge of the natural history of HCV. In the univariable analysis, there was no statistically significant difference in knowledge of HCV natural history by HIV or HCV status (Table 4). However, knowledge was associated with having at least a high school diploma, (OR: 1.46, 95% CI: 1.08, 1.98), history of sharing needles (OR: 1.86, 95% CI: 1.27, 2.75), and knowing between 10 and 19 other PWID (OR: 1.65, 95% CI: 1.02, 2.67) or at least 50 other PWID (OR: 1.82, 95% CI: 1.20, 2.78). In the first multivariable analysis, having at least a high school diploma (aOR:1.41, 95% CI: 1.02, 1.95) and history of sharing needles (aOR: 2.04, 95% CI: 1.32, 3.15) remained significantly associated with higher knowledge. Additionally, female sex was associated with lower knowledge (aOR: 0.66, 95% CI: 0.46, 0.96). In the second multivariable model, only the association between lifetime history of sharing needles (aOR: 1.76, 95% CI: 1.10, 2.83) and high natural history knowledge was significant.

HCV Treatment Knowledge

Overall, 78% of the ALIVE participants correctly answered the three treatment-related questions. In univariable analysis, compared to HCV mono-infected participants, HCV negative participants were significantly less likely to have high knowledge of HCV treatment (OR: 0.27, 95% CI: 0.19, 0.39) (Table 5). Additionally, participants who self-reported injecting drugs in the previous 6-months had 50% (95% CI: 0.27, 0.92) lower odds of a high treatment knowledge

score. Participants who were prescribed medication for opioid use disorder in the previous 6-months had 50% (95% CI: 1.02, 2.26) higher odds of high treatment knowledge. In the multivariable analyses that accounted for lifetime risk factors (aOR: 0.27, 95% CI: 0.17, 0.39) and recent risk behaviors (aOR: 0.22, 95% CI: 0.14, 0.36), the association between being HCV negative and lower treatment knowledge persisted. Finally, the association between baseline drug use and lower treatment knowledge (aOR: 0.51, 95% CI: 0.26, 0.98) was statistically significant, but the association between drug use at follow-up and treatment knowledge as not.

HCV Knowledge among Subgroups of PWID

When evaluating whether HCV knowledge differed among HIV positive PWID by HIV viral suppression, we observed no differences (Supplemental Table 1a). Similarly, among HCV-infected participants, knowledge of HCV transmission or natural history did not appear to vary by engagement in HCV care. However, knowledge of HCV treatment was significantly higher among participants who were aware of their HCV-positive status or treated for HCV in the past (Supplemental Table 1b). After restricting the analysis, results showed that participants who were diagnosed with HCV prior to entering the study, but not treated, had over 3-times the odds of high treatment knowledge, compared to those who were not diagnosed before their baseline visit, in both multivariable models (Supplemental Table 2).

DISCUSSION

Our study showed that, overall, HCV knowledge among this population of people who inject drugs (PWID) is high, although critical gaps remain. Encouragingly, nearly all participants were aware of which injection-related drug use practices contributed to HCV transmission. Likewise, nearly all participants were aware that HCV could negatively affect your liver over time, but two-thirds correctly estimated the percentage of people who would develop liver cancer or liver

disease, similar to findings from the interferon era.[40–42] We observed substantial improvement with respect to HCV treatment knowledge with 80% of the participants correctly answering that HCV is curable. This was remarkably higher than results from a prior study among ALIVE participants in the interferon-era, which found that 70% were aware that treatment was available, but only one-fifth of those correctly answered that HCV is curable.[27] Despite this marked improvement, a relatively high percentage of participants had incorrect beliefs regarding treatment duration or side effects. This is likely representative of residual misinformation about changes between interferon-based and DAA treatment. If so, these results suggest specific HCV-related topics that should be highlighted in education efforts for PWID.

In addition to assessing overall gaps in knowledge, we identified some factors that could be considered facilitators to obtaining knowledge of DAAs, specifically. It was encouraging that HCV treatment knowledge was higher among those who were aware of their HCV infection prior to completing the survey. In fact, this has also been observed in other studies, which found that HCV knowledge was higher among HCV infected PWID who were either diagnosed, evaluated or treated before an HCV knowledge assessment.[31,32,43] This suggests that people are being counseled about treatment at the point of testing or at some point afterwards, which is critical for effective linkage to care. Additionally, PWID may be more receptive to information regarding treatment after they are diagnosed with HCV, when it is perceived to be more relevant. However, in this population between 35% and 40% of those who were HCV infected were unaware of their infection at study entry. This stresses the importance of ensuring adequate information about HCV transmission risk and treatment is available to all PWID, as many are not yet aware of their status and some may acquire HCV in the future.

We hypothesized that proximity and usage of services and social network size could impact HCV knowledge because contact with people or these systems have the potential for knowledge provision. In fact, this has been confirmed in both interferon and DAA-era studies

among PWID.[31,42–48] While we failed to detect associations between service utilization, social network size and knowledge of HCV transmission, we did observe that a larger social network size and prescription of medication for opioid use disorder were associated with higher knowledge of HCV natural history and treatment, respectively. Our study did not capture whether participants attribute their HCV knowledge to either of these mechanisms, but these associations may still provide some insight into places where PWID can obtain knowledge. However, it should be noted that the measure of healthcare utilization and treatment for opioid use capture usage within the past six months only and it is possible that a participant could have received HCV education more than six months ago.

To achieve HCV elimination goals in the United States, there have been widespread campaigns to improve awareness of HCV, its sequalae, and treatment modalities, including at services that are frequented by PWID. However, the quality of education across these settings may vary. Our study supports that knowledge among PWID has substantially increased soon after the availability of DAAs. At the same time, our study also demonstrated that residual information related to interferon-based treatment remains. These results can be used to update HCV education materials that are not only tailored to PWID, but also healthcare professionals and other direct service providers who work with PWID. For example, updated education materials could highlight that DAA-based therapies have shorter duration, fewer frequency of treatment-related side effects and the low pill burden, compared to interferon-based therapies.

Our study is not without limitations. First, participants were not asked where or when they received HCV education, which impacts our ability to draw conclusions regarding utilization of services and HCV knowledge. Second, while HIV and HCV status are laboratory confirmed, participants self-report drug use practices, engagement in HCV care, and HCV treatment history. We do not anticipate this to bias our results, as previous studies in ALIVE have shown high validity and reliability of participants' self-report drug use.[49] There is the potential for

selection bias, as HCV mono-infected participants were less likely to return for the first follow-up visit. We addressed this by performing a multivariable regression using variables from the baseline visit, which did not change any of our findings. Finally, since this study was conducted in a large cohort study, our findings may not be generalizable to other areas or broader PWID community in Baltimore, MD. However, since HCV knowledge questions are asked prior to the receipt of HCV counseling at ALIVE, we believe that baseline knowledge is likely generally representative to that of PWID in Baltimore.

Despite the availability of DAAs, HCV treatment uptake among PWID in the US remains low. In the interferon-era poor knowledge of HCV was a common barrier among PWID. Our study showed an improvement in PWID knowledge, but misinformation remains, which could be a contributing factor as to why treatment uptake remains low today. Our study results can help modernize HCV education and focus these initiatives to groups at high-risk of poor HCV knowledge. Both could be a critical step to improve treatment uptake among this community.

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Table 1. Characteristics of 826 ALIVE participants who completed an HCV knowledge survey by HCV and HIV status, Baltimore, MD, 2015-2018

	HCV Mono-infected	HCV Negative	HIV/HCV Coinfected	p-value
N	447	264	115	
Demographic Characteristics[1]				
Age (year), median (IQR)	47.0 (37.8, 54.3)	41.4 (31.0, 48.4)	53.2 (45.5, 57.9)	<0.01
Female sex	139 (31.1%)	62 (23.5%)	36 (31.3%)	0.08
Black race	212 (47.4%)	142 (53.8%)	93 (80.9%)	<0.01
Education level ≥high school diploma	233 (52.1%)	151 (57.2%)	52 (45.6%)	0.11
Social Network Factors[1]				
Number of known PWID in Baltimore City				
0-9	89 (19.9%)	61 (23.1%)	24 (20.9%)	0.17
0-19	84 (18.8%)	53 (20.1%)	17 (14.8%)	
20-49	107 (23.9%)	74 (28.0%)	25 (21.7%)	
≥50	167 (37.4%)	76 (28.8%)	49 (42.6%)	
Number of known PWID with HCV infection in Baltimore City				
0-1	112 (25.3%)	60 (23.1%)	30 (26.1%)	0.94
2-4	100 (22.6%)	67 (25.8%)	30 (26.1%)	
5-14	114 (25.7%)	68 (26.2%)	28 (24.3%)	
≥15	117 (26.4%)	65 (25.0%)	27 (23.5%)	
Drug Use Behaviors				
Any injection drug use[1]	392 (89.3%)	233 (89.3%)	88 (78.6%)	<0.01
Type of drug use[2]				<0.01
None	34 (11.6%)	10 (5.5%)	16 (16.3%)	
Injection drug use only[3]	31 (10.6%)	15 (8.2%)	9 (9.2%)	
Non-injection drug use only[4]	30 (10.2%)	20 (10.9%)	26 (26.5%)	
Injection drug use and non-injection drug use	198 (67.6%)	138 (75.4%)	47 (48.0%)	
Frequency of injection drug use[2]				<0.01
None	59 (18.3%)	35 (17.0%)	37 (35.2%)	
Less than daily	110 (34.1%)	70 (34.0%)	31 (29.5%)	
Daily	154 (47.7%)	101 (49.0%)	37 (35.2%)	
Prescribed medication for opioid use disorder[2]	245 (75.2%)	130 (63.1%)	67 (63.8%)	<0.01
Visited syringe services program[2]	134 (41.7%)	86 (41.7%)	38 (36.2%)	0.57
Ever shared needles[1]	372 (83.4%)	167 (63.7%)	98 (85.2%)	<0.01
Healthcare Utilization[2]				
Had a primary care provider	247 (76.0%)	156 (75.7%)	101 (96.2%)	<0.01
Outpatient visit	212 (65.0%)	132 (64.1%)	97 (93.3%)	<0.01
Emergency department visit	145 (44.8%)	86 (41.7%)	50 (47.6%)	0.59
Proximity to Harm Reduction[1]				
Closest substance use treatment facility (km), median (IQR)	0.5 (0.2, 1.0)	0.5 (0.2, 1.1)	0.4 (0.2, 0.8)	0.22
HCV Care Continuum				
Ever tested for HCV	427 (96.4%)	234 (90.4%)	109 (95.6%)	<0.01
Ever tested HCV positive	274 (64.3%)		65 (59.6%)	<0.01
Evaluated by a medical provider that treats HCV	104 (54.7%)		40 (81.6%)	<0.01
Ever treated for HCV	36 (8.2%)		31 (27.9%)	<0.01
Completion of Previous Treatment and Successfully Cured[5]	2 (22.2%)		2 (66.7%)	0.38

[1]From baseline visit (N-826)
[2]From follow-up visit (N=637) and reflective of 6 months prior to study visit
[3]Includes injection of heroin, cocaine, speedball (heroin and cocaine together), methamphetamine or any other type of drug
[4]Includes smoking crack or heroin
[5]Of the HCV mono-infected participants, 1 (50%) participant who self-reported being cured had an undetectable HCV viral load
Of HIV/HCV coinfected participants, both (100%) participants who self-reported completing treatment had detectable HCV viral loads

Table 2. Results of a 17-item HCV knowledge scale among 826 ALIVE participants, Baltimore, MD, 2015-2018

Question	Correct Answer	Total Correct Answers	HCV Negative	HCV Mono-Infected	HIV/HCV Coinfected	p-value
Transmission Subscale[1]						
You can get hepatitis C by kissing someone who has hepatitis C	False	635 (77.5%)	176 (68.2%)	363 (81.9%)	94 (82.5%)	<0.01
You can get hepatitis C by having sex with someone who has hepatitis C if there is no blood to blood contact	False	387 (47.2%)	113 (43.6%)	219 (49.4%)	54 (47.4%)	0.33
You can get hepatitis C by being stuck with a needle or sharp instrument that has hepatitis C infected blood on it	True	798 (97.3%)	254 (98.1%)	430 (97.1%)	110 (96.5%)	0.62
You can get hepatitis C by sharing injecting needles, syringes, with someone who has hepatitis C, even if only a few times	True	808 (98.5%)	256 (98.8%)	436 (98.4%)	112 (98.2%)	0.87
You can get hepatitis C by sharing injecting spoons, water or cookers with someone who has hepatitis C, even if only a few times	True	732 (89.3%)	218 (84.2%)	406 (91.6%)	106 (93.0%)	<0.01
You can get hepatitis C by getting a blood transfusion from an infected donor	True	789 (96.2%)	252 (97.3%)	423 (95.5%)	110 (96.5%)	0.47
You can get hepatitis C by being born to a woman who had hepatitis C when she gave birth	True	563 (68.7%)	184 (71.0%)	301 (67.9%)	75 (65.8%)	0.54
Natural History Subscale[2]						
Someone with hepatitis C can look and feel fine	True	797 (97.4%)	249 (96.1%)	432 (97.5%)	112 (99.1%)	0.21
If someone is infected with the hepatitis C virus, they will most likely carry the virus all their lives	True	479 (58.6%)	158 (61.0%)	255 (57.6%)	63 (56.3%)	0.60
Infection with the hepatitis C virus can cause the liver to stop working	True	779 (95.3%)	237 (91.9%)	429 (97.1%)	109 (96.5%)	<0.01
Someone with a positive hepatitis C antibody result today can test negative for hepatitis C antibodies in the future	False	217 (26.6%)	77 (29.7%)	103 (23.4%)	36 (31.9%)	0.07
Almost everyone with chronic hepatitis C infection will develop liver failure or liver cancer in the future	False	288 (35.3%)	89 (34.4%)	162 (36.7%)	36 (31.9%)	0.58
Treatment Subscale[3]						
Hepatitis C infection can be cured	True	653 (79.9%)	172 (66.4%)	376 (85.6%)	102 (91.1%)	<0.01
Hepatitis C treatments cause bad side effects in almost everyone who takes them	False	489 (59.9%)	137 (52.9%)	276 (62.6%)	74 (65.5%)	0.02
Hepatitis C can be cured with just a couple of pills a day taken for 12 weeks	True	503 (61.6%)	106 (40.9%)	307 (69.6%)	87 (77.0%)	<0.01
People who inject drugs should get the hepatitis A and B vaccine whether or not they have hepatitis C	True	675 (82.5%)	205 (79.2%)	366 (82.8%)	101 (89.4%)	0.06
A hepatitis C vaccine is available	False	76 (9.3%)	25 (9.7%)	42 (9.5%)	8 (7.1%)	0.70

[1]The cut-point for a high knowledge score was 86% and 23% of those who completed the HCV assessment had high transmission knowledge
[2]The cut-point for a high knowledge score was 80% and 31% of those who completed the HCV assessment had high natural history knowledge
[3]The cut-point for a high knowledge score was answering all 3-questions correctly, and 78% of those who completed the HCV assessment had high treatment knowledge

Table 3. Correlates of relatively high HCV transmission knowledge[1] among participants of ALIVE study by HIV and HCV status, Baltimore, MD, 2015-2018

	Univariable Analysis	Baseline Model[2]	Follow-Up Model[3]
	OR (95% Conf. Interval)	aOR (95% Conf. Interval)	aOR (95% Conf. Interval)
HCV and HIV status[4]			
HCV mono-infected	REF	REF	REF
HCV negative	0.77 (0.53, 1.12)	0.71 (0.46, 1.07)	0.73 (0.46, 1.18)
HIV/HCV coinfected	0.74 (0.45, 1.22)	0.86 (0.49, 1.49)	0.91 (0.50, 1.64)
Age (year)[4]	0.98 (0.96, 0.99)	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
Participant's sex[4]			
Male	REF	REF	REF
Female	0.96 (0.67, 1.37)	0.99 (0.67, 1.46)	0.91 (0.59, 1.41)
Participant's race[4]			
Non-Black	REF	REF	REF
Black	0.68 (0.48, 0.94)	0.95 (0.63, 1.43)	1.01 (0.64, 1.60)
≥High school diploma[4]			
No	REF	REF	REF
Yes	1.12 (0.81, 1.54)	1.01 (0.71, 1.43)	1.04 (0.70, 1.55)
Ever shared needles[4]			
No	REF	REF	REF
Yes	1.54 (1.01, 2.34)	1.39 (0.87, 2.21)	1.35 (0.80, 2.28)
Number of known PWID in Baltimore City[4]			
0-9	REF	REF	REF
10-19	1.59 (0.97, 2.61)	1.57 (0.92, 2.68)	1.56 (0.87, 2.80)
20-49	1.10 (0.68, 1.79)	1.10 (0.65, 1.85)	0.96 (0.54, 1.72)
>=50	0.90 (0.57, 1.43)	0.88 (0.53, 1.46)	0.66 (0.37, 1.16)
Any injection drug use			
No	REF	REF	
Yes	1.70 (0.97, 2.98)	1.26 (0.70, 2.27)	
Injection drug use frequency			
None	REF		REF
Less than daily	1.81 (1.02, 3.21)		1.49 (0.82, 2.70)
Daily	1.85 (1.07, 3.19)		1.50 (0.84, 2.68)
Prescribed of medication for opioid use disorder			
No	REF		REF
Yes	1.21 (0.80, 1.84)		1.05 (0.67, 1.63)
Outpatient visit			
No	REF		REF
Yes	0.86 (0.58, 1.29)		1.05 (0.67, 1.64)
Closest substance use treatment facility (km)[4]	0.98 (0.87, 1.11)	0.93 (0.81, 1.07)	0.90 (0.75, 1.08)

[1]Knowledge score was generated from 7 transmission-related questions out of 17-item HCV knowledge scale. The cut-point for a high knowledge score was 86% and 23% of those who completed the HCV assessment had high transmission knowledge
[2]Model includes variables that were collected at baseline visit (N-826)
[3]Model contains variables that were collected at follow-up visit (N=637) and reflective of 6 months prior to study visit
[4]Variable is included in all multivariable models, regardless of statistical significance in univariable analysis

Table 4. Correlates of relatively high HCV natural history knowledge[1] among participants of ALIVE study by HIV and HCV status, Baltimore, MD, 2015-2018

	Univariable	Baseline Model[2]	Follow-Up Model[3]
	OR (95% Conf. Interval)	aOR (95% Conf. Interval)	aOR (95% Conf. Interval)
HCV and HIV status[4]			
HCV mono-infected	REF	REF	REF
HCV negative	1.12 (0.81, 1.56)	1.35 (0.93, 1.97)	1.33 (0.87, 2.03)
HIV/HCV coinfected	1.03 (0.66, 1.61)	0.96 (0.59, 1.56)	0.86 (0.51, 1.45)
Age (year)[4]	1.00 (0.99, 1.02)	1.01 (1.00, 1.03)	1.00 (0.99, 1.03)
Participant's sex[4]			
Male	REF	REF	REF
Female	0.71 (0.51, 1.00)	0.66 (0.46, 0.96)	0.72 (0.48, 1.07)
Participant's race[4]			
Non-Black	REF	REF	REF
Black	0.85 (0.63, 1.15)	0.88 (0.60, 1.28)	0.82 (0.54, 1.25)
≥High school diploma[4]			
No	REF	REF	REF
Yes	1.46 (1.08, 1.98)	1.41 (1.02, 1.95)	1.31 (0.92, 1.87)
Ever shared needles[4]			
No	REF	REF	REF
Yes	1.86 (1.27, 2.75)	2.04 (1.32, 3.15)	1.76 (1.10, 2.83)
Number of known PWID in Baltimore City[4]			
0-9	REF	REF	REF
10-19	1.65 (1.02, 2.67)	1.51 (0.91, 2.52)	1.53 (0.87, 2.70)
20-49	1.16 (0.73, 1.85)	1.11 (0.68, 1.81)	1.14 (0.66, 1.98)
>=50	1.82 (1.20, 2.78)	1.53 (0.97, 2.42)	1.38 (0.83, 2.29)
Any injection drug use			
No	REF	REF	
Yes	1.01 (0.64, 1.59)	1.01 (0.62, 1.66)	
Injection drug use frequency			
None	REF		REF
Less than daily	0.85 (0.53, 1.34)		0.86 (0.52, 1.40)
Daily	0.73 (0.47, 1.13)		0.77 (0.48, 1.25)
Prescribed of medication for opioid use disorder			
No	REF		REF
Yes	0.76 (0.53, 1.08)		0.68 (0.46, 1.01)
Outpatient visit			
No	REF		REF
Yes	1.44 (0.99, 2.10)		1.49 (0.98, 2.29)
Closest substance use treatment facility (km)[4]	0.97 (0.86, 1.09)	0.95 (0.84, 1.08)	0.96 (0.85, 1.09)

[1]Knowledge score generated from 5 natural history related questions out of 17-item HCV knowledge scale. The cut-point for a high knowledge score was 80% and 31% of those who completed the HCV assessment had high natural history knowledge

[2]Model includes variables that were collected at baseline visit (N-826)

[3]Model contains variables that were collected at follow-up visit (N=637) and reflective of 6 months prior to study visit

[4]Variable is included in all multivariable models, regardless of statistical significance in univariable analysis

Table 5. Correlates of high HCV treatment knowledge[1] among participants of ALIVE study by HIV and HCV status, Baltimore, MD, 2015-2018

	Univariable	Baseline Model[2]	Follow-Up Model[3]
	OR (95% Conf. Interval)	aOR (95% Conf. Interval)	aOR (95% Conf. Interval)
HCV and HIV status[4]			
HCV mono-infected	REF	REF	REF
HCV negative	0.27 (0.19, 0.39)	0.26 (0.17, 0.39)	0.22 (0.14, 0.36)
HIV/HCV coinfected	1.63 (0.83, 3.20)	1.46 (0.73, 2.94)	1.40 (0.67, 2.91)
Age (year)[4]	1.02 (1.00, 1.03)	1.00 (0.98, 1.02)	1.00 (0.98, 1.03)
Participant's sex[4]			
Male	REF	REF	REF
Female	1.02 (0.71, 1.47)	0.95 (0.63, 1.43)	1.05 (0.66, 1.66)
Participant's race[4]			
Non-Black	REF	REF	REF
Black	0.92 (0.65, 1.29)	0.90 (0.58, 1.39)	0.83 (0.51, 1.36)
≥High school diploma[4]			
No	REF	REF	REF
Yes	1.03 (0.74, 1.44)	1.08 (0.74, 1.56)	1.16 (0.76, 1.76)
Ever shared needles[4]			
No	REF	REF	REF
Yes	1.70 (1.17, 2.47)	1.06 (0.68, 1.64)	1.06 (0.64, 1.74)
Number of known PWID in Baltimore City[4]			
0-9	REF	REF	REF
10-19	0.89 (0.53, 1.49)	0.83 (0.47, 1.46)	0.80 (0.41, 1.55)
20-49	0.83 (0.51, 1.35)	0.85 (0.49, 1.45)	0.74 (0.39, 1.39)
>=50	1.13 (0.71, 1.81)	0.93 (0.55, 1.56)	0.79 (0.44, 1.44)
Any injection drug use			
No	REF	REF	
Yes	0.50 (0.27, 0.92)	0.51 (0.26, 0.98)	
Injection drug use frequency			
None	REF		REF
Less than daily	0.69 (0.40, 1.19)		0.70 (0.38, 1.28)
Daily	0.74 (0.43, 1.25)		0.78 (0.43, 1.40)
Prescribed of medication for opioid use disorder			
No	REF		REF
Yes	1.51 (1.02, 2.26)		1.35 (0.87, 2.11)
Outpatient visit			
No	REF		REF
Yes	0.89 (0.59, 1.36)		0.68 (0.42, 1.10)
Closest substance use treatment facility (km)[4]	0.98 (0.87, 1.09)	1.01 (0.90, 1.13)	0.98 (0.86, 1.11)

[1]Knowledge score generated from 3 treatment-related questions out of 17-item HCV knowledge scale. The cut-point for a high knowledge score was answering all 3-questions correctly, and 78% of those who completed the HCV assessment had high treatment knowledge
[2]Model includes variables that were collected at baseline visit (N-826)
[3]Model contains variables that were collected at follow-up visit (N=637) and reflective of 6 months prior to study visit
[4]Variable is included in all multivariable models, regardless of statistical significance in univariable analysis

Supplemental Table 1a. Proportion of participants with HIV/HCV coinfection with high HCV knowledge by HIV viral suppression

Knowledge Scale	Undetectable HIV Viral Load	Detectable HIV Viral Load	p-value
High Transmission Knowledge	11 (22.0%)	12 (15.6%)	0.36
High Natural History Knowledge	15 (30.6%)	26 (33.8%)	0.71
High Treatment Knowledge	43 (87.8%)	64 (83.1%)	0.48

Supplemental Table 1b. Proportion of participants with high knowledge by HCV diagnosis and treatment status

Knowledge Scale	HCV Infected, Not Diagnosed	HCV Infected, Diagnosed, Not Treated	HCV Infected, Diagnosed, Treated	p-value
High Transmission Knowledge	87 (22.3%)	81 (26.8%)	8 (20.5%)	0.33
High Natural History Knowledge	121 (31.0%)	98 (32.6%)	11 (28.2%)	0.82
High Treatment Knowledge	272 (69.6%)	263 (87.4%)	38 (97.4%)	<0.01

Supplemental Table 2. Correlates of high HCV treatment knowledge[1] among HCV-infected participants by awareness of HCV status upon study entry, Baltimore, MD, 2015-2018

	Baseline Model[2]	Follow-up Model[3]
	aOR (95% Conf. Interval)	aOR (95% Conf. Interval)
HCV status upon study entry[4]		
HCV infected, not diagnosed	REF	REF
HCV infected, diagnosed, not treated	3.00 (1.93, 4.66)	3.05 (1.86, 5.00)
Age (year)[4]	1.01 (0.99, 1.03)	1.03 (1.00, 1.05)
Participant's sex[4]		
Male	REF	REF
Female	0.96 (0.62, 1.48)	1.13 (0.69, 1.85)
Participant's race[4]		
Non-Black	REF	REF
Black	0.84 (0.54, 1.32)	0.73 (0.43, 1.21)
≥High school diploma[4]		
No	REF	REF
Yes	1.00 (0.67, 1.47)	1.12 (0.72, 1.75)
Ever shared needles[4]		
No	REF	REF
Yes	1.24 (0.78, 1.96)	1.19 (0.71, 2.01)
Number of known PWID in Baltimore City[4]		
0-9	REF	REF
10-19	0.56 (0.30, 1.06)	0.50 (0.24, 1.04)
20-49	0.58 (0.32, 1.07)	0.48 (0.24, 0.97)
>=50	0.63 (0.35, 1.13)	0.51 (0.26, 1.00)
Any injection drug use		
No	REF	
Yes	0.57 (0.29, 1.12)	
Injection drug use frequency		
None		REF
Less than daily		0.75 (0.40, 1.41)
Daily		0.77 (0.41, 1.43)
Prescribed of medication for opioid use disorder		
No		REF
Yes		1.44 (0.90, 2.30)
Outpatient visit		
No		REF
Yes		0.58 (0.35, 0.99)
Closest substance use treatment facility (km)[4]	1.03 (0.90, 1.17)	1.00 (0.87, 1.14)

[1]Knowledge score generated from 3 treatment-related questions out of 17-item HCV knowledge scale and is based on highest quartile of responses. % with high knowledge

[2]Model includes variables that were collected at baseline visit (N-826)

[3]Model contains variables that were collected at follow-up visit (N=637) and reflective of 6 months prior to study visit

[4]Variable is included in all multivariable models, regardless of statistical significance in univariable analysis

Chapter 4. Evaluating temporal trends and changes in predictors of HCV treatment uptake in the interferon and direct acting antiviral eras among people who inject drugs (PWID) in Baltimore, Maryland

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ABSTRACT

Background: HCV treatment uptake among people who inject drugs (PWID) was low in the interferon-era and barriers to treatment were well characterized. With the availability of direct acting antivirals (DAA), treatment uptake among PWID has improved. But as evident by the increasing incidence of acute HCV infection, subgroups of PWID are missed.

Methods: We evaluated cumulative HCV treatment uptake among 1,146 HCV-antibody positive participants of the ALIVE study, a community-based cohort of current and former PWID, who were eligible for HCV treatment and had at least one visit between 2011 and 2019. We first calculated the cumulative proportion of HCV treatment uptake and treatment rate for each year of the study to understand temporal trends over time. Subsequently, we categorized the study period into three eras of HCV treatment, the interferon-era (2011-2013), the early DAA-era (2014-2016), and late DAA-era (2017-2018) to evaluate how characteristics of participants treated changed. Finally, we performed a Poisson regression analysis to identify predictors of HCV treatment uptake in each era.

Results: The cumulative proportion of HCV treatment uptake increased from 15% in the interferon-era to 70% the late DAA-era. The greatest improvement was seen in the DAA-era, from 2014-2019, where the rate of HCV treatment uptake improved from 0.68 per 100 person-years in 2014 to 6.63 per 100 person-years in 2019. In the interferon-era, education level was the main predictor of treatment uptake (IRR: 2.69, 95% CI: 1.27, 5.73). In the early DAA-era, predictors of treatment uptake included older age (IRR: 1.05, 95% CI: 1.02, 1.07), having a recent outpatient visit (IRR: 1.15, 95% CI: 1.34, 3.76), having HIV/HCV coinfection with an undetectable HIV viral load (IRR: 1.87, 95% CI: 1.42, 2.48), and having cirrhosis (IRR: 1.64, 95% CI: 1.16, 2.32). In the late DAA-era, the main predictors of treatment uptake were being HIV/HCV coinfected with a detectable HIV viral load (IRR: 0.35, 95% CI: 0.16, 0.77) and having

a recent outpatient visit (IRR: 2.24, 95% CI: 1.56, 3.77). Daily injection drug use (IRR: 0.60, 95% CI: 0.38, 0.97) was a predictor in the univariable analysis, but the association did not persist in the adjusted analysis.

Conclusion: Treatment uptake improved remarkably over the entire study period. Those at-risk of poor treatment uptake today include PWID that are disconnected from the healthcare system and injecting drugs daily. These PWID are at the highest risk of HCV transmission and reinfection but will likely be hardest to reach.

INTRODUCTION

Hepatitis C virus (HCV) is the most prevalent bloodborne viral infection in the United States.[1,2] Injection drug use (IDU) remains the most common mode of transmission and prevalence of HCV among people who inject drugs (PWID) is upwards of 90%.[3–5] Prevalence of HCV is highest among those born between 1945 and 1965, many of whom are former PWID, older, minority, and live in urban areas. These individuals were infected when HCV incidence peaked in 1980s and 1990s and are now experiencing the long-term complications of HCV-related morbidity and mortality.[6,7] From 1992 to 2005, HCV incidence declined, largely due to primary prevention measures, like screening of blood donations and syringe service programs. After plateauing for 5-years, HCV incidence has increased steadily since 2010. In fact, between 2010 and 2018 incident cases of acute HCV infection more than quadrupled.[8–10] These cases are primarily attributed to shared injection practices, among a younger, increasingly female, and white population who live in suburban and rural areas of the US.[11,12]

However, HCV is curable and in 2014, remarkable new therapeutics, direct acting antivirals (DAA), became available.[13,14] DAA-based treatment requires a single pill, taken daily, for as little as 8-weeks, resulting in minimal adverse events, and cure rates of >98%.[15–19] Conversely, prior to late 2013, HCV treatment required weekly injections of interferon and high pill burden, which resulted in serious adverse events that were experienced by >75% of those who were treated.[20–22] Furthermore, treatment could last for up to 48-weeks and roughly half of those who started interferon-based treatment were cured.[20,21] Because of the burden of HCV in the United States and availability of DAAs, in 2015, the World Health Organization and National Academies of Sciences, Engineering, and Medicine released two goals to achieve HCV elimination globally and in the United States by 2030: to decrease HCV incidence by 90% and HCV-related mortality by 65%.[23,24]

Treatment uptake with interferon-based therapies was low among PWID.[25–28] In addition to fear of treatment-related side effects, PWID experienced additional barriers, such as stigma, provider willingness, poor knowledge of treatment, and competing priorities.[29,30] As a result, many chose to forego treatment altogether or wait until more effective and better tolerated therapies became available. However, due to their high cost, most state Medicaid plans quickly implemented restrictions that limited access to DAAs in 2014.[31] While implementation of these restrictions was variable across states, they included documentation of advanced liver fibrosis; 6-months abstinence of substance use; and HCV medication could only be prescribed through a hepatologist, gastroenterologist or infectious disease specialist. Since then, insurance restrictions have relaxed in many states, in part due to pressure from advocacy groups, legal action, and a growing evidence-base showing the benefits of treating those with mild and moderate fibrosis. For example, in 2017, Maryland's Medicaid plan removed the 6-month sobriety restriction and enabled primary care providers and other non-infectious disease specialists to prescribe HCV medication.[31] Two years later, they reduced the fibrosis cut-off for Medicaid reimbursement from moderate fibrosis to mild.[31,32]

Treatment uptake among PWID has improved in areas where insurance restrictions were relaxed and among those who are engaged in specialty healthcare or PWID-related services.[33–36] But there are still groups with limited access. Studies evaluating barriers to DAA treatment initially focused on structural barriers relating to early insurance restrictions, but have since expanded to include both provider and patient-level factors.[37–40] However, this body of research has focused largely on persons in care and consistently miss PWID who are disconnected from these types of services. Certain barriers from the interferon-era, like stigma and distrust of the healthcare system, likely persisted into the DAA-era. But it is possible that other individual-level barriers between the groups are different. As a result, the aim of our study is to evaluate temporal trends in HCV treatment uptake between 2011 and 2019 among a community-based

cohort of PWID to identify ongoing individual-level barriers to treatment, even as restrictions to accessing treatment are removed.

METHODS

Study Population

The ALIVE (AIDS Linked to the IntraVenous Experience) Study is a community-based cohort of current and former PWID, ongoing since 1988 and previously described elsewhere.[41] As a community-based cohort, participants are recruited primarily through street outreach, flyer distribution and peer referrals. Recruitment has spanned more than three decades: 1988-1989 (N=2,946), 1994-1995 (N=434), 1997-1998 (N=295), 2005-2008 (N=1,009), and 2015-2018 (N=674). Eligible participants are ≥18 years of age with a history of injection drug use. In total, 5,358 individuals have been enrolled in ALIVE. This analysis includes 1,146 HCV-antibody positive participants who had at least one study visit 2011-2019 and had either a positive HCV RNA test or self-reported HCV treatment.

Data Measurement

At entry into the cohort, ALIVE participants self-reported demographic characteristics, lifetime drug use, and medical history. Subsequently, participants were followed semi-annually, at which time they were asked about drug use, comorbidities, and healthcare utilization within the previous 6-months, frequency of IDU within the past 30 days, and a FibroScan was performed on all participants to measure liver stiffness (fibrosis).[42] Results were categorized as: no or mild fibrosis (<8 kPa), significant fibrosis (8 kPa-12.3 kPa), or cirrhosis (>12.3 kPa).[43,44] For this study, we considered sociodemographic characteristics (e.g., sex, race, age, education level, and homelessness status) as they had been previously associated with treatment uptake, variables that captured the insurance restrictions (e.g., fibrosis score, type of insurance, and

recent drug use), services associated with improved treatment uptake (e.g., outpatient medical visits, HIV specialty care, prescription of medication for opioid use disorder) and medical comorbidities, a known barrier to treatment in the past.[29,30,34,39,45–54] All variables, except sociodemographic characteristics reflect use in the previous 6-months. A participant was considered homeless if they self-reported being displaced for at least one night. An undetectable HIV viral load was used as an indicator for engagement in HIV specialty care, among participants who were HIV/HCV coinfected. To quantify medical comorbidities, we created a health index based on the number of chronic conditions that a participant reported having at each visit, including diabetes, seizures, high cholesterol, hypertension, stoke, kidney disease, chronic lung disease, depression, anxiety, bipolar disorder or schizophrenia. To measure depression, we used participant responses to the 20-item Center for Epidemiologic Studies – Depression (CESD) survey to measure depressive symptoms in the previous week.[56,57] A score of 23 or greater indicated severe depressive symptomology.[57] Participants were screened for HIV at each study visit using an enzyme-linked immunosorbent assay (ELISA) and Geenius HIV 1/2 Confirmatory Assay (Bio-Rad, Hercules, California). An HIV RNA test (Roche, Basel, Switzerland) was performed on HIV-positive participants at each visit to determine HIV viral suppression (≤50 copies/mL). All participants were screened for HCV antibodies using an ELISA (Ortho Clinical Diagnostics, Raritan, NJ) and an HCV RNA test (Abbott Molecular, Des Plaines, Ill) confirmed chronicity. HCV RNA testing was conducted annually on HCV-positive participants with additional testing to confirm cure among participants who self-reported initiating HCV treatment between visits.

Outcome Ascertainment

The outcome of interest, HCV treatment, was based on whether a participant self-reported being treated for HCV, either “ever” or “in the last 6-months.” There was some variability in this measurement over time. Prior to June 2013, participants were only asked about HCV treatment

if they reported being aware of treatment and that they had been offered treatment by a medical provider. Beginning in June 2013, all participants, regardless of confirmed HCV status, awareness of treatment or a provider offer of treatment were asked if they received HCV treatment. Throughout the study period, participants were asked if they were “ever” treated for HCV or treated “in the last 6-months,” at baseline and follow-up visits, respectively. A follow-up question was added in 2013 and only asked to participants who reported “ever” treated at their baseline visit, clarifying if treatment was in the 6-months prior to that visit. For the purposes of this study, participants who reported being treated “in the last 6-months” (at either baseline or follow-up visits) were considered treated during follow-up. Participants who only reported being “ever” treated were considered treated before our analysis.

Statistical Analysis

We used descriptive statistics to characterize participants with ALIVE study visits between 2011 and 2019 using a Chi-square or Fisher’s exact test to compare categorical variables and a Wilcoxon-Mann-Whitney test for continuous variables. First, we compared the sociodemographic, drug use, and health-related characteristics of people who reported treatment prior to our analysis (N=84), to those treated during follow-up (N=488), and those never treated for HCV (N=574). In order to evaluate how characteristics of those treated for HCV during the study period changed, we restricted the sample to participants that reported being treated during follow-up and compared the same characteristics for three time-periods. These periods were chosen to capture treatment uptake in the different eras of HCV treatment modalities: the interferon (INF) era (2011-2013), when treatment required interferon injections; early in the availability of DAAs (2014-2016) when insurance companies had the harshest restrictions, which included a sobriety window, prescription of medication by a specialist, and documentation of advanced liver disease; and the later DAA-era (2017-2019) when the sobriety and specialist restrictions were removed and the fibrosis restriction was relaxed. For participants

who had two or more visits per year, we used drug use, healthcare utilization, and comorbidities reported at the first visit. If a participant had a visit in January or February, they were considered treated in the previous calendar year.

To evaluate temporal changes in treatment uptake, we calculated cumulative treatment uptake both as the proportion of those treated and as a rate per person-time for each year of study period. First, we calculated the cumulative proportion of participants who reported being treated for each year. The denominator included all those eligible for treatment, as well as, those treated in the year, plus those who reported treatment in prior years of the study period. The numerator included the people who reported treatment at a visit in the year, plus all in the years prior, totaling 572 for the entire study period. When calculating the annual treatment rate, we excluded participants who were treated prior to our analysis. The denominator was the person-years of follow-up time between study visits for each year, contributed by all those who were eligible for treatment, but had not been treated, and those who reported treatment in the previous 6-months. For participants who reported HCV treatment, we assumed that treatment occurred halfway between visits and contributed the corresponding amount of person-time. The numerator was the number of participants who were treated each year of follow-up, totaling 488 participants over the 2011-2019 study period.

For our primary analysis, we used Poisson regression analysis to calculate incidence rate ratios of HCV treatment uptake stratified by the three time-periods to understand predictors of HCV treatment uptake in each era. Variables considered for the final model included sociodemographic characteristics, health-related variables, and drug use practices. To account for temporality between healthcare utilization and HCV treatment, we lagged the outpatient medical visit by one study visit so that it reflects a participant's healthcare utilization 6-12 months before they reported being treated for HCV. Variables considered for the final model

were based on *a priori* knowledge of factors associated with HCV treatment uptake or had p-values <0.1 in the univariable analysis.

Finally, because the most recent enrollment cohort had less follow-up than prior cohorts, we conducted sensitivity analyses for the DAA-era and calculated both the cumulative HCV treatment uptake, as well as annual HCV treatment rates for 2015 through 2019, stratified by when a participant was recruited into the study, pre-2005, 2005-2008, 2015-2018. Subsequently, we repeated the Poisson regression for the late DAA-era (2017-2019), to compare how predictors of HCV treatment uptake varied by enrollment period.

RESULTS

Characteristics of Study Population

Characteristics of the 1,146 participants included in the study are presented in Table 1. Overall, the median age was 52.7 years (IQR: 47.2, 57.3), 69% (n=791) were male, and 83.3% (n=955) were Black. Of the 1,146 participants with evidence of prior HCV infection, 50% (N=572) reported receiving any treatment for HCV. Among those who were treated, 14.7% (N=84) were prior to the analysis and 85.3% (N=488) reported being treated during follow-up. Among the 488 participants, nearly half had at least a high school education or equivalency (n=233, 47.7%), 73% had cirrhosis (n=356, 73.0%), and 64.5% (n=314) had injected drugs within the 6-months prior to entering the study. Of those who were not treated for HCV (N=574), 70.4% (n=404) had HCV mono-infection and 22% had no or mild fibrosis (n=126). Finally, the 84 treated prior to the analysis were more likely to be HIV/HCV coinfected with an undetectable HIV viral load (n=38, 45.2%), as well as, have at least two other chronic diseases (n=59, 70.2%), compared to those who were never treated or treated during follow-up.

Temporal Changes of HCV Treatment Uptake

Overall, HCV treatment uptake improved throughout the study period. Figure 1 shows that cumulative treatment uptake increased from 15% of the population being treated in 2011 to 70% in 2019, a 4.7-fold increase. Among those who were treatment naïve at entry into the study/analysis, the rate of HCV treatment uptake was lowest in the interferon-era, ranging from 0.08 per 100 person-years in 2011 to 0.44 per 100 person-years in 2013 (Figure 2). There was a 3.9-fold increase between 2014 (0.68 per 100) and 2015 (2.68 per 100 person-years), the first two years of the early DAA-era. After an initial peak in 2015, the treatment rate dropped until 2017 after which point there was a 3.4-fold increase to reach 6.63 per 100 person-years in 2019.

Characteristics of Participants Receiving HCV Treatment during Study Period

Characteristics of the 488 participants who were treated during the study period are presented in Table 2, stratified by time-period. Only 6.5% (N=54) of those with visits in the interferon-era reported HCV treatment. Of those who did, 85.2% (n=46) were Black, 16.7% (n=9) reported any recent non-injection drug use, and 79.6% (n=43) did not report any injection drug use in the prior 6-months. In terms of healthcare-related characteristics, 46.3% (n=25) had Medicaid, 51.9% (n=28) were HCV mono-infected, and 68.5% (n=37) had cirrhosis. Roughly one-quarter (N=210) of those with visits in the early DAA-era reported being treated for HCV. Characteristics of those who were treated were similar to those treated in the interferon-era in terms of injection drug use (n=167, 79.5%), being insured through Medicaid (n=98, 46.9%), being HCV mono-infected (n=106, 50.5%), and having cirrhosis (n=147, 70.0%). However, a larger percentage were Black (n=202, 96.2%) and had reported non-injection drug use in the previous 6-months (n=48, 22.9%). One-third (N=224) with visits in the late DAA-era were treated for HCV. Of them 79.9% (n=179) were Black, 45.5% (n=102) reported recent non-injection drug use and 61.4% (n=137) reported not injecting drugs in the last 6-months. A larger percentage had Medicaid

insurance (n=138, 61.6%) and HCV mono-infection (n=151, 67.4%), but fewer had cirrhosis (n=98, 43.8%), compared to the other two treatment eras.

Associations between Covariates and Rate of HCV Treatment Uptake

Correlates of HCV treatment uptake for the three time-periods are presented in Table 3. In the interferon era, the rate of treatment uptake was 2.81 (95% CI: 1.30, 6.07) times higher among those with at least a high school diploma or GED compared to those who had not completed high school in the univariable analysis. The association persisted (IRR: 2.69, 95% CI: 1.27, 5.73) after adjusting for demographics, healthcare utilization, comorbidities, and recent drug use. No other factors were significantly associated with HCV treatment uptake for that time-period.

In the early DAA-era, Black race (IRR: 3.33, 95% CI: 1.50, 7.43) and having an outpatient visit 6-12 months before reporting being treated for HCV (IRR: 2.90, 95% CI: 1.78, 4.73) were significantly associated with HCV treatment uptake in univariable analysis. The rate of treatment uptake also increased with age (IRR: 1.06, 95% CI: 1.04, 1.08), having at least one chronic comorbidity (IRR: 1.63, 95% CI: 1.05, 2.52), cirrhosis (IRR: 1.69, 95% CI: 1.19, 2.38), and being HIV/HCV coinfected with an undetectable HIV viral load (IRR: 2.10, 95% CI: 1.61, 2.74). In the multivariable model, age (IRR: 1.05, 95% CI: 1.02, 1.07), having an outpatient visit (IRR: 2.25, 95% CI: 1.34, 3.76), having cirrhosis (IRR: 1.64, 95% CI: 1.16, 2.32), and being HIV/HCV coinfected with an undetectable HIV viral load (IRR: 1.87, 95% CI: 1.42, 2.48) remained significantly associated with having a higher HCV treatment uptake.

In the later DAA-era, being female (IRR: 0.66, 95% CI: 0.47, 0.93) and injecting drugs daily (IRR: 0.60, 95% CI: 0.38, 0.97) were associated with lower HCV treatment uptake, while having an outpatient visit 6-12 months before reporting HCV treatment was associated with 2.43 (95% CI: 1.58, 3.73) times treatment uptake in univariable analysis. In multivariable analysis, the

associations between treatment uptake and being female (IRR: 0.65, 95% CI: 0.45, 0.92) and having an outpatient visit (IRR: 2.42, 95% CI: 1.56, 3.77) remained significant. We also found that the treatment rate was 65% (95% CI: 0.16, 0.77) lower if the participant was HIV/HCV coinfected with a detectable HIV viral load compared to HCV mono-infected participants.

In sensitivity analyses, we compared treatment uptake by recruitment cohort to ensure that treatment uptake was not driven by participants more recently recruited with limited follow-up (e.g., from 2015 and 2018). Results showed that treatment uptake was consistent across the cohorts (see supplemental materials).

DISCUSSION

Our study demonstrated that among this population of people who inject drugs (PWID), HCV treatment uptake improved from 15% being treated in the interferon-era to 70% in the late DAA-era. In this cohort, treatment uptake remained <5% for more than two decades.[30] However in our study, half of the participants reported being treated for HCV over this 9-year period. The most dramatic improvement in treatment uptake occurred following the availability of direct acting antivirals (DAA). Initially, the increase in HCV treatment was slow, but it increased remarkably from 2014 to 2019, likely reflecting the greater number of DAAs available and relaxed insurance restrictions over time. However, some barriers to HCV treatment remain in this population and in order to achieve ambitious elimination goals, many more will need to be treated and these barriers will have to be addressed.

The observed trends in treatment uptake were consistent with findings in other populations and PWID. Overall, in the interferon-era, it was estimated that only 16% of those with HCV infection initiated treatment and less than 10% of PWID, specifically.[25–28,58] In fact, we found that only 7% of those eligible for treatment were treated in the 2011-2013 interferon-era time period. This

increased to 25% in the early DAA-era and 35% in the late DAA-era. Those more likely to be treated in the early DAA-era were older, had advanced liver disease, and were already engaged in the healthcare system. Compared to the other two treatment periods, in the late DAA-era, treatment uptake improved among participants with recent drug use and those with mild or no liver fibrosis. These trends in treatment uptake are similar to other populations and likely reflect the impact of DAA-based therapies, as well as the implementation and relaxation of insurance restrictions.[31,32,39,59–61]

HCV is a slow progressing, largely asymptomatic, disease.[62] It takes 25-30 years for roughly 30% of those with chronic HCV infection to develop cirrhosis, the most severe stage of fibrosis.[62] Despite having Medicaid fibrosis restrictions in the later DAA-era, we found that older age and having cirrhosis were not predictors of HCV treatment uptake, as they were in the early DAA-era. In fact, the percentage of those treated who had mild or no fibrosis more than doubled from 19% to 44% between the early and late DAA eras, respectively. There are a few ways to explain this observation. First, the fibrosis restriction was unique to Medicaid and 40% of the participants treated had either Medicare, private insurance, or insurance through the Veterans Administration, which was not subject to the same restrictions. Second, insurance companies and treatment guidelines prioritize treatment among those with severe liver fibrosis and non-decompensated cirrhosis.[39,63,64] As a result, those with advanced liver fibrosis would be treated first, once DAAs became available. Because these people were successfully treated in the early DAA-era, it would decrease the proportion of individuals who were eligible for HCV treatment and had cirrhosis in the late DAA-era.

To achieve HCV elimination among PWID, we must first identify which PWID are not accessing HCV treatment and develop strategies to reach them. We found that healthcare utilization was the greatest predictor of treatment uptake in the late DAA period. Additionally, our findings indicated that daily injection drug use was the main barrier to treatment in the late DAA period.

For this study, we did not ask participants why they were not treated for HCV. As a result, we cannot definitively conclude why active PWID were not treated as often as former PWID. Poor treatment uptake among active PWID is likely a combination of individual and provider-level barriers. Provider reluctance to treat people with current or former substance use was a barrier in the interferon period, with providers citing fear of poor treatment adherence or reinfection.[65,66] Despite interferon and DAA-era studies showing similar cure rates among PWID with recent or active drug use compared to those not using drugs, some providers are still reticent about treating active PWID.[66–68] It is possible that provider stigma associated with active drug use remains a persistent barrier among active PWID who are motivated to be treated today. In terms of individual-level barriers, like in the interferon-era, it is also possible that HCV treatment is a lower priority when a person is actively injecting drugs with high frequency.[29] These uncertainties highlight the need for future investigations to understand non-treatment among this group.

Our study is not without limitations. First, given the longitudinal nature of the study, selection bias due to losses to follow-up could be a concern. In particular, since we included participants from all recruitment cohorts in this analysis, there is a potential for survivor bias. For example, participants who were older or HIV/HCV coinfected are more likely to experience HCV-related mortality. As a result, our sample may include participants who were healthier than the larger PWID community. However, we do not think survivor bias will threaten the internal validity of our results, as our sensitivity analysis showed treatment uptake was consistent across recruitment cohorts and our main findings are consistent to those of other studies. Second, other than HIV and HCV status and liver fibrosis, other variables, including our outcome, HCV treatment, are based on self-report. We do not anticipate that this will result in biased associations, as other studies have validated self-reported treatment initiation with HCV RNA testing.[69] Finally, Maryland relaxed its Medicaid's fibrosis restriction in 2019, which was also the end of our study

period. As a result, our study did not have sufficient follow-up time after its implementation to capture changes in treatment uptake resulting from the modification. We expect that treatment uptake will continue to improve because of it.

In conclusion, it was encouraging that half of this population of current and former PWID had been treated for HCV, of which, 85% was between 2011-2019. However, we did identify characteristics associated with not being treated, namely daily injection drug use and poor healthcare utilization. Both were barriers in the interferon-era and persist today. Initiating HCV treatment among this population is and will continue to be difficult for a variety of reasons. However, HCV elimination goals are unachievable without doing so. Our work highlights the need for future studies to identify which specific individual-level barriers are preventing these subgroups from initiating treatment. These results can, in turn, be used to inform interventions and strategies to ensure universal access to HCV treatment among all PWID.

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Table 1. Characteristics of 1,146 HCV-antibody positive participants by self-reported HCV treatment status anytime from 2011-2019

	Never treated for HCV	Treated during follow-up	Treated prior to analysis	p-value
N	574	488	84	
Demographic Characteristics				
Age (year), median (IQR)	52.1 (45.5, 56.5)	53.5 (48.9, 57.9)	53.4 (47.0, 59.2)	<0.01
Female sex	209 (36.4%)	130 (26.6%)	16 (19.0%)	<0.01
Black race	464 (80.8%)	427 (87.5%)	64 (76.2%)	<0.01
Education level ≥high school diploma	230 (40.2%)	233 (47.7%)	30 (35.7%)	0.02
Homeless or displaced[1]	107 (18.7%)	69 (14.1%)	15 (17.9%)	0.13
Drug Use Practices[1]				
Any non-injection drug use[2]	208 (36.2%)	166 (34.0%)	36 (42.9%)	0.28
Frequency of injection drug use				
None	337 (58.9%)	314 (64.5%)	43 (51.2%)	
Less than daily	119 (20.8%)	103 (21.1%)	17 (20.2%)	0.01
Daily	116 (20.3%)	70 (14.4%)	24 (28.6%)	
Any alcohol use	309 (54.0%)	260 (53.4%)	37 (44.0%)	0.23
Visited syringe services program	100 (17.5%)	62 (12.7%)	17 (20.2%)	0.05
Prescribed medication for OUD[3,4]	223 (38.9%)	167 (34.2%)	30 (35.7%)	0.29
Co-Morbidities and Healthcare Utilization				
Type of health insurance[1]				
Medical Assistance	288 (50.3%)	233 (47.9%)	40 (48.2%)	
Medicare or other insurance[5]	238 (41.6%)	216 (44.4%)	40 (48.2%)	0.52
Uninsured	46 (8.0%)	37 (7.6%)	3 (3.6%)	
Visited the emergency department[1]	185 (32.3%)	129 (26.4%)	33 (39.3%)	0.02
At least one outpatient visit[1]	394 (68.8%)	357 (73.3%)	66 (78.6%)	0.09
HIV status/HIV viral suppression[6]				
HCV mono-infected	404 (70.4%)	287 (58.8%)	39 (46.4%)	
Coinfected & undetectable HIV	96 (16.7%)	151 (30.9%)	38 (45.2%)	<0.01
Coinfected & detectable HIV	74 (12.9%)	50 (10.2%)	7 (8.3%)	
Fibrosis score[7]				
None or Mild Fibrosis	126 (22.0%)	101 (20.7%)	14 (16.7%)	
Significant Fibrosis	50 (8.7%)	31 (6.4%)	11 (13.1%)	0.18
Cirrhosis	398 (69.3%)	356 (73.0%)	59 (70.2%)	
Health index[8]				
No comorbidities	116 (20.2%)	101 (20.7%)	17 (20.2%)	
1 comorbidity	105 (18.3%)	103 (21.1%)	8 (9.5%)	0.13
≥2 comorbidities	353 (61.5%)	284 (58.2%)	59 (70.2%)	
Depressive symptoms (CESD>23)[1]	154 (26.9%)	115 (23.6%)	23 (27.4%)	0.43
Recruitment Cohort				
1988-1989	192 (33.4%)	166 (34.0%)	21 (25.0%)	
1994-1995[9]	94 (16.4%)	70 (14.3%)	5 (6.0%)	<0.01
2005-2008	176 (30.7%)	144 (29.5%)	22 (26.2%)	
2015-2018	112 (19.5%)	108 (22.1%)	36 (42.9%)	

[1]Reflective of 6 months prior to study visit

[2]Includes smoking crack or heroin

[3]Prior to 2014, participants who reported seeking substance use treatment were asked if it was part of a methadone maintenance program only. Starting in 2014, all participants were asked if they were prescribed methadone, buprenorphine or Naltrexone

[4]OUD is abbreviation of opioid use disorder

[5]Insurances included were Medicare, private insurance, insurance through the Affordable Care Act, Veterans Administration, Ryan White, or any other type

[6]Viral suppression is defined as ≤50 copies per mL

[7]None or mild fibrosis defined as <8 kPa, significant fibrosis defined as 8-12.3 kPa, cirrhosis defined as ≥12.3 kPa

[8]Based on if a participant reported ever being diagnosed or diagnosed in previous 6-months for any of the following: diabetes (high blood sugar), seizures (epilepsy or convulsions), high cholesterol, hypertension (high blood pressure), stroke, kidney (kidney) disease or failure, chronic lung disease (asthma, COPD, emphysema, not pneumonia), depression, anxiety or panic disorder, bipolar disorder, schizophrenia/schizoaffective disorder

[9]Participants recruited in 1998 (N=52) were combined with the participants recruited 1994-1995 (N=117)

Table 2. Characteristics of 488 participants with chronic HCV infection who self-reported HCV treatment per year

	Interferon Era (2011-2013)[1]	DAA Era with Strict Restrictions (2014-2016)	Later Availability of DAAs (2017-2019)	p-value
N	54 (6.5%)[2]	210 (25.1%)[2]	224 (34.8%)[2]	
Demographic Characteristics				
Age (year), median (IQR)	54.1 (49.1, 57.9)	58.2 (54.2, 62.7)	56.9 (51.3, 61.6)	<0.01
Female sex	14 (25.9%)	53 (25.2%)	63 (28.1%)	0.79
Black race	46 (85.2%)	202 (96.2%)	179 (79.9%)	<0.01
≥High school diploma	29 (53.7%)	95 (45.2%)	109 (48.7%)	0.50
Homeless or displaced[3]	7 (13.0%)	15 (7.1%)	23 (10.3%)	0.32
Drug Use Practices[3]				
Any non-injection drug use[4]	9 (16.7%)	48 (22.9%)	102 (45.5%)	<0.01
Frequency of injection use				
None	43 (79.6%)	167 (79.5%)	137 (61.4%)	
Less than daily	8 (14.8%)	23 (11.0%)	47 (21.1%)	<0.01
Daily	3 (5.6%)	20 (9.5%)	39 (17.5%)	
Any alcohol use	20 (37.0%)	90 (42.9%)	112 (50.2%)	0.13
Visited syringe services program	2 (3.7%)	18 (8.6%)	44 (19.7%)	<0.01
Prescribed medication for OUD[5,6]	15 (27.8%)	96 (45.7%)	140 (62.5%)	<0.01
Co-Morbidities and Healthcare Utilization				
Type of health insurance[3]				
Medical Assistance	25 (46.3%)	98 (46.9%)	138 (61.6%)	
Medicare or other insurance[7]	26 (48.1%)	109 (52.2%)	85 (37.9%)	<0.01
Uninsured	3 (5.6%)	2 (1.0%)	1 (0.4%)	
Emergency department visit[3]	12 (22.2%)	56 (26.7%)	66 (29.5%)	0.53
Outpatient visit last 6-12 months	16 (76.2%)	166 (89.2%)	153 (83.2%)	0.11
HIV status/HIV viral suppression[8]				
HCV mono-infected	28 (51.9%)	106 (50.5%)	151 (67.4%)	
Coinfected & undetectable HIV	23 (42.6%)	91 (43.3%)	60 (26.8%)	<0.01
Coinfected & detectable HIV	3 (5.6%)	13 (6.2%)	13 (5.8%)	
Liver fibrosis[9]				
None or mild fibrosis	17 (31.5%)	40 (19.0%)	98 (43.8%)	
Significant fibrosis	0 (0.0%)	23 (11.0%)	28 (12.5%)	<0.01
Cirrhosis	37 (68.5%)	147 (70.0%)	98 (43.8%)	
Health index[10]				
No comorbidities	6 (11.1%)	31 (14.8%)	36 (16.1%)	
1 comorbidity	10 (18.5%)	60 (28.6%)	43 (19.2%)	0.12
≥2 comorbidities	38 (70.4%)	119 (56.7%)	145 (64.7%)	
Depressive symptoms (CESD>23)[3]	17 (31.5%)	40 (19.0%)	66 (29.6%)	0.02
Recruitment Cohort				
1988-1989	25 (46.3%)	88 (41.9%)	53 (23.7%)	
1994-1995[11]	8 (14.9%)	35 (16.6%)	27 (12.1%)	<0.01
2005-2008	21 (38.9%)	64 (30.5%)	59 (26.3%)	
2015-2018	0 (0.0%)	23 (11.0%)	85 (37.9%)	

[1]8 participants were classified as being treated in 2010 because they reported HCV treatment in previous 6-months at an ALIVE visit in January or February 2011

[2]Percentage of unique participants who were eligible for HCV treatment in each treatment period: Interferon Era (2011-2013) – 830 participants; Early DAA Era 2014-2016) – 836 participants; Late DAA Era (2017-2019) – 644 participants

[3]Reflective of 6 months prior to study visit

[4]Includes smoking crack or heroin

[5]Prior to 2014, participants who reported seeking substance use treatment were asked if it was part of a methadone maintenance program only. Starting in 2014, all participants were asked if they were prescribed methadone, buprenorphine or Naltrexone

[6]OUD is abbreviation of opioid use disorder

[7]Insurances included were Medicare, private insurance, insurance through the Affordable Care Act, Veterans Administration, Ryan White, or any other type

[8]Viral suppression is defined as ≤50 copies per mL

[9]None or mild fibrosis defined as <8 kPa, significant fibrosis defined as 8-12.3 kPa, cirrhosis defined as ≥12.3 kPa

[10]Based on if a participant reported ever being diagnosed or diagnosed in previous 6-months for any of the following: diabetes (high blood sugar), seizures (epilepsy or convulsions), high cholesterol, hypertension (high blood pressure), stroke, kidney (kidney) disease or failure, chronic lung disease (asthma, COPD, emphysema, not pneumonia), depression, anxiety or panic disorder, bipolar disorder, schizophrenia/schizoaffective disorder

[11]Participants recruited in 1998 (N=26) were combined with the participants recruited 1994-1995 (N=44)

Table 3. Correlates of HCV treatment uptake by HCV treatment time-period among ALIVE participants, Baltimore MD, 2011-2019

Characteristic	Interferon Era (2011-2013)		DAA Era with Strict Restrictions (2014-2016)		Later Availability of DAAs (2017-2019)	
	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
Age (year)	0.99 (0.94, 1.03)	0.99 (0.95, 1.04)	1.06 (1.04, 1.08)	1.05 (1.02, 1.07)	1.01 (0.99, 1.02)	0.99 (0.97, 1.01)
Participant's sex						
Male	REF	REF	REF	REF	REF	REF
Female	1.13 (0.52, 2.44)	1.18 (0.54, 2.57)	0.75 (0.56, 1.02)	0.76 (0.56, 1.03)	0.66 (0.47, 0.93)	0.65 (0.45, 0.92)
Participant's race						
non-Black	REF	REF	REF	REF	REF	REF
Black	0.56 (0.19, 1.61)	0.63 (0.17, 2.32)	3.33 (1.50, 7.43)	2.00 (0.88, 4.55)	0.96 (0.65, 1.42)	1.07 (0.64, 1.77)
≥High school diploma						
No	REF	REF	REF	REF	REF	REF
Yes	2.81 (1.30, 6.07)	2.69 (1.27, 5.73)	1.29 (1.00, 1.67)	1.29 (1.00, 1.66)	1.35 (1.00, 1.81)	1.29 (0.94, 1.78)
Frequency of injection drug use[1]						
None	REF	REF	REF	REF	REF	REF
Less than daily	1.20 (0.46, 3.16)	1.23 (0.46, 3.32)	0.66 (0.40, 1.07)	0.75 (0.46, 1.21)	1.03 (0.69, 1.53)	1.08 (0.72, 1.63)
Daily	0.41 (0.06, 3.03)	0.51 (0.07, 3.60)	0.71 (0.42, 1.18)	0.88 (0.53, 1.47)	0.60 (0.38, 0.97)	0.66 (0.41, 1.06)
Prescribed medication for OUD[1,2,3]						
No	REF		REF		REF	
Yes	1.47 (0.68, 3.18)		0.84 (0.64, 1.10)		1.11 (0.82, 1.51)	
Type of health insurance[1]						
Medical Assistance	REF		REF		REF	
Medicare or other insurance[4]	1.36 (0.61, 3.04)		1.23 (0.93, 1.64)		1.10 (0.81, 1.49)	
Uninsured	1.22 (0.26, 5.69)		0.36 (0.09, 1.49)		0.48 (0.15, 1.59)	
Outpatient visit last 6-12 months						
No	REF	REF	REF	REF	REF	REF
Yes	1.61 (0.66, 3.94)	1.39 (0.54, 3.61)	2.90 (1.78, 4.73)	2.25 (1.34, 3.76)	2.43 (1.58, 3.73)	2.42 (1.56, 3.77)
HIV status/HIV viral suppression[5]						
HCV mono-Infected	REF	REF	REF	REF	REF	REF
Coinfected & undetectable HIV	1.81 (0.83, 3.93)	1.81 (0.79, 4.13)	2.10 (1.61, 2.74)	1.87 (1.42, 2.48)	1.50 (1.06, 2.13)	1.34 (0.93, 1.92)
Coinfected & detectable HIV	0.77 (0.18, 3.37)	0.84 (0.20, 3.58)	1.07 (0.61, 1.86)	1.28 (0.73, 2.24)	0.36 (0.17, 0.77)	0.35 (0.16, 0.77)
Liver fibrosis[6]						
None or Mild Fibrosis	REF	REF	REF	REF	REF	REF
Significant Fibrosis	0.33 (0.04, 2.57)	0.32 (0.04, 2.51)	1.07 (0.61, 1.87)	0.98 (0.56, 1.74)	0.80 (0.48, 1.34)	0.73 (0.43, 1.24)
Cirrhosis	0.89 (0.42, 1.89)	0.91 (0.43, 1.95)	1.69 (1.19, 2.38)	1.64 (1.16, 2.32)	0.95 (0.69, 1.30)	0.89 (0.64, 1.23)
Health index[7]						
No comorbidities	REF		REF		REF	
1 comorbidity	2.43 (0.63, 9.41)		1.63 (1.05, 2.52)		1.18 (0.73, 1.91)	
≥2 comorbidities	2.39 (0.71, 8.08)		1.18 (0.80, 1.75)		1.07 (0.72, 1.60)	

[1]Reflective of 6 months prior to study visit

[2]Prior to 2014, participants who reported seeking substance use treatment were asked if it was part of a methadone maintenance program only. Starting in 2014, all participants were asked if they were prescribed methadone, buprenorphine or Naltrexone

[3]OUD is abbreviation of opioid use disorder

[4]Insurances included were Medicare, private insurance, insurance through the Affordable Care Act, Veterans Administration, Ryan White, or any other type

[5]Viral suppression is defined as ≤50 copies per mL

[6]None or mild fibrosis defined as <8 kPa, significant fibrosis defined as 8-12.3 kPa, cirrhosis defined as ≥12.3 kPa

[7]Based on if a participant reported ever being diagnosed or diagnosed in previous 6-months for any of the following: diabetes (high blood sugar), seizures (epilepsy or convulsions), high cholesterol, hypertension (high blood pressure), stroke, kidney (kidney) disease or failure, chronic lung disease (asthma, COPD, emphysema, not pneumonia), depression, anxiety or panic disorder, bipolar disorder, schizophrenia/schizoaffective disorder

Supplemental Table 1. Correlates of HCV treatment uptake by ALIVE cohort in the later DAA-era, Baltimore MD, 2017-2019

Characteristic	Pre-2005 Cohort		2005-2008 Cohort		2015-2018 Cohort	
	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
Age (year)	1.02 (0.98, 1.06)	0.98 (0.94, 1.03)	1.01 (0.97, 1.04)	0.99 (0.95, 1.03)	1.01 (0.98, 1.04)	1.01 (0.97, 1.05)
Participant's sex						
Male	REF	REF	REF	REF	REF	REF
Female	0.64 (0.37, 1.11)	0.61 (0.35, 1.07)	0.43 (0.23, 0.82)	0.47 (0.23, 0.93)	1.14 (0.65, 2.00)	1.06 (0.59, 1.90)
Participant's race						
Non-Black	REF	REF	REF	REF	REF	REF
Black	2.26 (0.57, 8.94)	3.02 (0.71, 12.90)	1.06 (0.54, 2.10)	1.40 (0.63, 3.10)	0.84 (0.49, 1.46)	0.58 (0.25, 1.35)
≥High school diploma						
No	REF	REF	REF	REF	REF	REF
Yes	1.22 (0.76, 1.96)	1.34 (0.80, 2.24)	1.85 (1.07, 3.20)	1.81 (0.97, 3.26)	0.98 (0.57, 1.67)	0.92 (0.52, 1.65)
Frequency of injection drug[1]						
None	REF	REF	REF	REF	REF	REF
Less than daily	1.16 (0.54, 2.49)	1.07 (0.48, 2.41)	0.79 (0.37, 1.72)	0.95 (0.43, 2.13)	0.72 (0.40, 1.29)	0.83 (0.45, 1.50)
Daily	0.94 (0.41, 2.15)	0.99 (0.41, 2.35)	0.85 (0.38, 1.91)	1.23 (0.56, 2.72)	0.21 (0.09, 0.49)	0.21 (0.09, 0.51)
Prescribed medication for OUD[1,2,3]						
No	REF		REF		REF	
Yes	0.97 (0.60, 1.56)		1.08 (0.61, 1.94)		1.30 (0.71, 2.40)	
Type of health insurance[1]						
Medical Assistance	REF		REF		REF	
Medicare or other insurance[4]	0.89 (0.55, 1.43)		1.49 (0.85, 2.60)		1.16 (0.64, 2.10)	
Uninsured	0.29 (0.04, 2.43)		0.62 (0.09, 4.27)		0.85 (0.10, 7.00)	
Outpatient visit last 6-12 months						
No	REF	REF	REF	REF	REF	REF
Yes	8.89 (2.79, 28.92)	10.15 (3.13, 32.87)	1.37 (0.71, 2.66)	1.39 (0.68, 2.84)	1.87 (0.94, 3.74)	1.66 (0.77, 3.60)
HIV status/HIV viral suppression[5]						
HCV Mono-Infected	REF	REF	REF	REF	REF	REF
Coinfected & undetectable HIV	1.52 (0.87, 2.65)	1.29 (0.72, 2.31)	1.87 (1.04, 3.38)	1.97 (1.05, 3.70)	1.26 (0.62, 2.58)	1.46 (0.65, 3.31)
Coinfected & detectable HIV	0.61 (0.20, 1.82)	0.56 (0.18, 1.77)	0.26 (0.06, 1.10)	0.30 (0.07, 1.31)	0.33 (0.08, 1.46)	0.35 (0.08, 1.50)
Liver fibrosis[6]						
None or Mild Fibrosis	REF	REF	REF	REF	REF	REF
Significant Fibrosis	1.07 (0.49, 2.31)	0.86 (0.38, 1.98)	0.60 (0.22, 1.64)	0.49 (0.18, 1.35)	0.77 (0.31, 1.90)	0.73 (0.29, 1.86)
Cirrhosis	0.70 (0.43, 1.16)	0.65 (0.39, 1.10)	1.18 (0.67, 2.09)	1.10 (0.63, 1.91)	1.25 (0.70, 2.23)	1.18 (0.63, 2.23)
Health index[7]						
No comorbidities	REF		REF		REF	
1 comorbidity	0.86 (0.41, 1.82)		1.64 (0.71, 3.76)		1.24 (0.49, 3.10)	
≥2 comorbidities	0.90 (0.48, 1.69)		1.17 (0.57, 2.39)		1.18 (0.58, 2.41)	

[1]Reflective of 6 months prior to study visit

[2]Prior to 2014, participants who reported seeking substance use treatment were asked if it was part of a methadone maintenance program only. Starting in 2014, all participants were asked if they were prescribed methadone, buprenorphine or Naltrexone

[3]OUD is abbreviation of opioid use disorder

[4]Insurances included were Medicare, private insurance, insurance through the Affordable Care Act, Veterans Administration, Ryan White, or any other type

[5]Viral suppression is defined as ≤50 copies per mL

[6]None or mild fibrosis defined as <8 kPa, significant fibrosis defined as 8-12.3 kPa, cirrhosis defined as ≥12.3 kPa

[7]Based on if a participant reported ever being diagnosed or diagnosed in previous 6-months for any of the following: diabetes (high blood sugar), seizures (epilepsy or convulsions), high cholesterol, hypertension (high blood pressure), stroke, kidney (kidney) disease or failure, chronic lung disease (asthma, COPD, emphysema, not pneumonia), depression, anxiety or panic disorder, bipolar disorder, schizophrenia/schizoaffective disorder

Figure 1. Cumulative HCV treatment uptake among ALIVE participants, Baltimore MD, 2011-2019

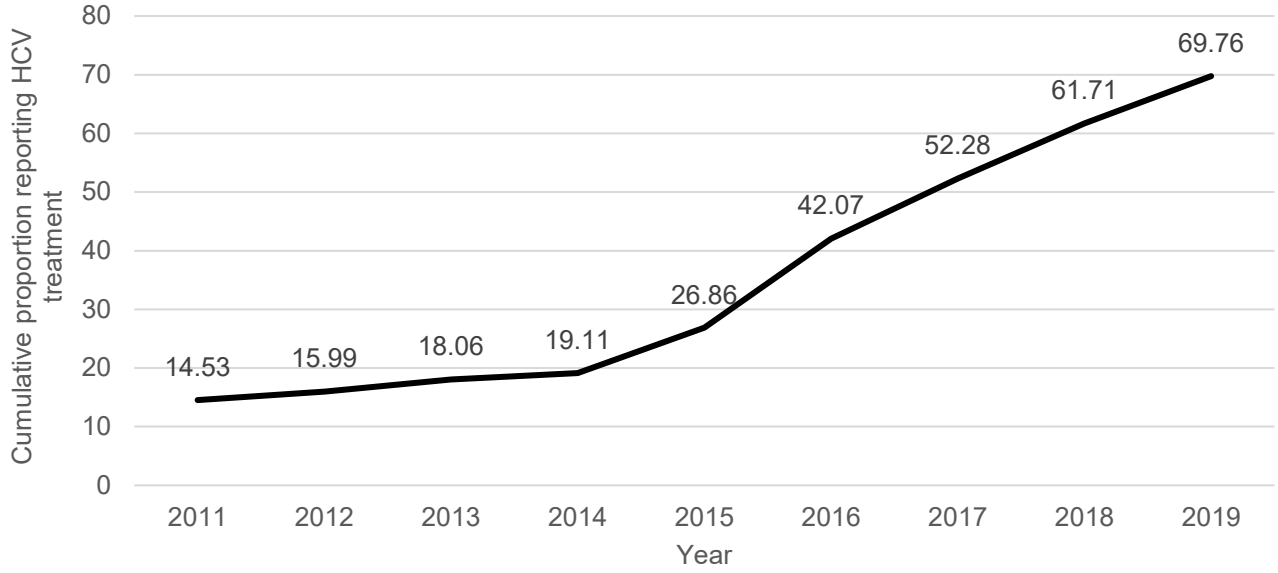
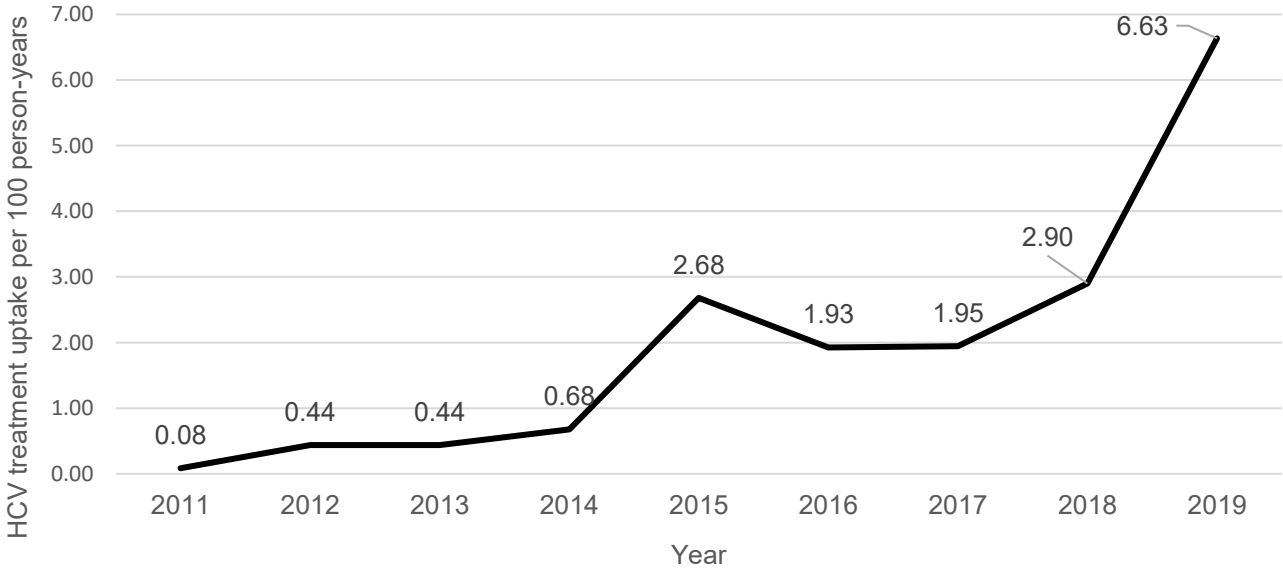
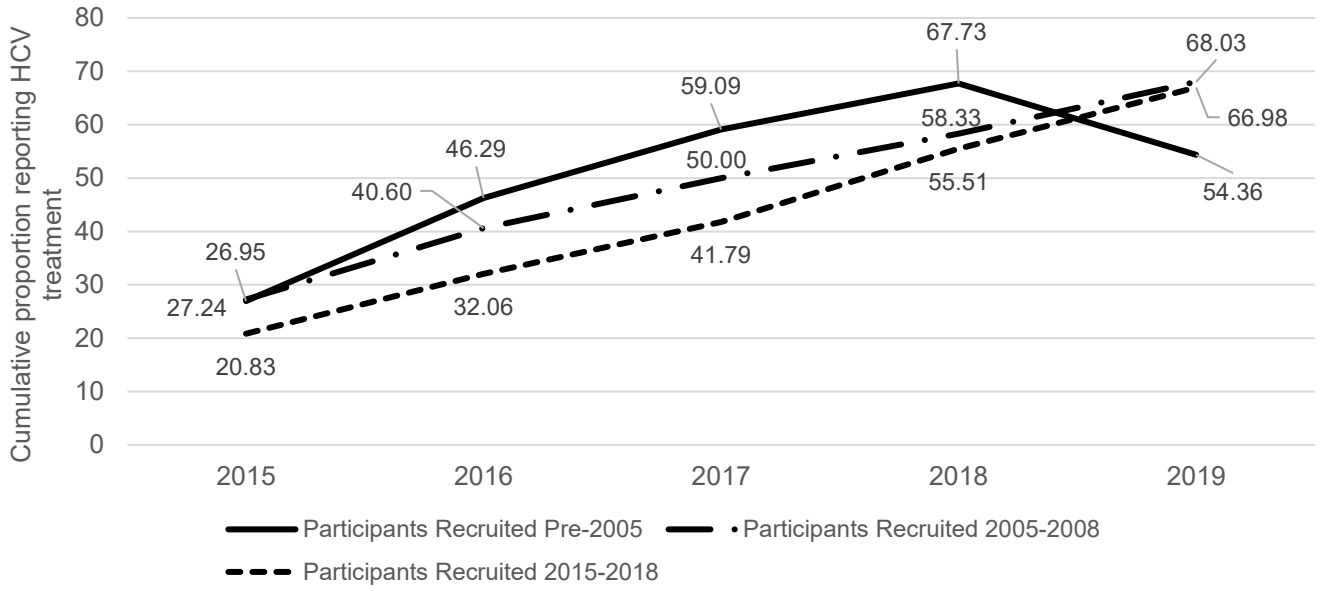


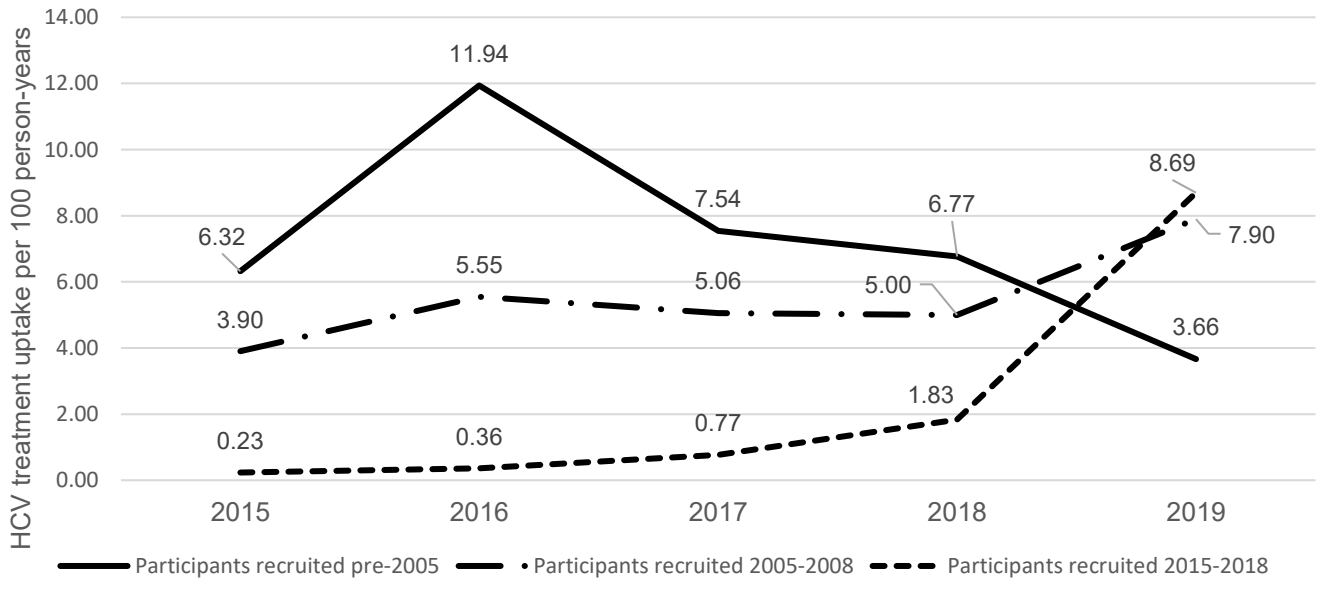
Figure 2. Annual rate of HCV treatment uptake among ALIVE participants, Baltimore MD, 2011-2019



Supplemental Figure 1. Cumulative HCV treatment uptake among ALIVE participants by recruitment cohort, Baltimore MD, 2015-2019



Supplemental Figure 2. Annual rate of HCV treatment uptake among ALIVE participants by cohort, Baltimore MD, 2015-2019



Chapter 5. Conclusions

In 2014, direct acting antiviral (DAA) agents became available and transformed hepatitis C virus (HCV) treatment. In the era of DAA therapies, efforts have been made to improve treatment uptake for HCV among people who inject drugs (PWID). While treatment uptake has, admittedly, improved among some PWID, the incidence of acute HCV infections has more than quadrupled between 2010 and 2018.[1] This indicates that there is still sufficient circulation of HCV within the PWID community reflecting that not enough PWID have been treated to curtail transmission. Studies that have sought to identify barriers to DAA treatment among PWID have largely focused on PWID who are either already engaged in healthcare or harm reduction services that facilitate HCV testing or care.[2–7] As a result, our knowledge base may not reflect the true burden of HCV, treatment need, and barriers within important groups of PWID who are perpetuating ongoing transmission. In this study, we used a multi-pronged approach to understand how treatment uptake has changed from the era of interferon-based therapies to the modern DAA-era of HCV therapy and identify subgroups of PWID who have not been treated to date. Furthermore, we sought to understand the extent to which specific barriers from the interferon-era persist today, how barriers from the interferon-era may be facilitators in the DAA-era, and emergent barriers specific to the DAA-era.

Summary of Findings

In Aim 1, we explored changes in treatment penetration throughout Baltimore City and Baltimore County by comparing the spatial distribution of HCV treatment need in three timepoints: interferon-era (2006-2007), early DAA-era (2015-2016), and late DAA-era (2017-2018). To do this, we identified statistically significant spatial clusters of higher than expected rates of HCV viremia, which was used as an indicator for treatment need. Finally, we characterized these

areas to help to understand whether clusters of HCV treatment need were explained best by characteristics of the individuals with HCV or the neighborhoods themselves. Overall, we found that the proportion of HCV viremia per Census tract declined significantly over the three study periods. There median proportion of viremia participants decreased from 83% in the interferon-era, 64% in the early DAA-era and a 39% in the later DAA time-period. Results from our cluster detection analysis identified a single cluster in the interferon-era (2006-2007) and two clusters in the early DAA-era (2015-2016). The interferon-era cluster was in Census tracts where the percentage of viremic participants was greater than 91% and were more likely to be in the most deprived neighborhoods. The two clusters in the early DAA-era were located in East and West Baltimore and we found that neighborhood deprivation, as well as individual race, were the strongest predictors of being in one of the clusters. However, we failed to identify any clusters in the later DAA-era. This study showed that by the late DAA-era, HCV treatment had penetrated all parts of the city. However, despite this, results also showed that treatment penetration was slower in areas of higher neighborhood deprivation and remains low in some places today. This signifies a need to investigate individual-level barriers that may explain this finding.

Aims 2 and 3 focused on individual-level barriers to HCV treatment. In Aim 2, we examined differences in HCV knowledge among 826 current and former PWID recruited in 2015-2018, by HIV and HCV status. Knowledge questions focused on modes of transmission, natural history, and treatment. We found that 23% of the participants had high knowledge of HCV transmission, 31% had high knowledge of HCV natural history, and 78% had high knowledge of HCV treatment. Almost all participants (>97%) were aware of which injection practices could result in transmission of HCV. Additionally, almost all participants knew that HCV negatively affects a person’s liver (95%), but that most people were asymptomatic (97%). Moreover, most persons (62%) were aware of oral therapies for DAAs. However, knowledge of DAA medications did vary by HIV/HCV status with the highest knowledge levels among HIV/HCV coinfected individuals

(77%), followed by HCV mono-infected individuals (70%), and, finally, HCV negative participants (41%). Additionally, less than two-thirds of the participants were aware that DAA treatment did not have severe side effects. Overall, there was variability in knowledge of HCV treatment by HIV and HCV status. Compared to HCV mono-infected participants, the odds of having a high treatment knowledge score among HCV negative and HIV/HCV coinfected participants was 0.22 (95% CI: 0.14, 0.36) and 1.40 (95% CI: 0.67, 2.91), respectively, adjusting for demographics, drug use, healthcare utilization, and social networks size. Moreover, among HCV-positive participants, we found that those who were aware of their HCV status prior to the ALIVE baseline visit had 3-times the odds of a high treatment score, compared to those who were diagnosed at baseline study visit. These findings demonstrate that, overall, HCV knowledge was high. While participants did not report where they were educated about HCV, findings from this study suggest that treatment may be discussed either at the time of or after their diagnosis of HCV. This underscores the importance of accurately describing the differences between interferon-based therapies and DAAs, as a way to promote HCV treatment.

In Aim 3, we evaluated temporal changes in treatment uptake among 1,146 HCV-infected participants, between 2011 and 2019, to understand how predictors and barriers to HCV treatment changed during the interferon and DAA eras. Overall, half of the participants reported being treated for HCV, of which, 488 (85%) reported treatment during the 2011-2019 study period. We found that treatment uptake improved greatly between the interferon and DAA eras. For example, cumulative treatment uptake increased 32% from 2011 until 2014. By comparison, it increased 265% from 2014 through 2019. We observed an initial peak in 2015, when the treatment rate increased from 0.7 per 100 person-years in 2014 to 2.7 per 100,000 person-years in 2015. The treatment rate declined slightly afterwards but increased to 6.6 per 100 person-years, a 129% increase from 2018.

The factors that explained treatment uptake also changed overtime. For example, when treatment uptake was lowest, in the interferon-era (2011-2013), education level was the only predictor of treatment uptake (IRR: 2.73, 95% CI: 1.29, 5.80), likely reflective of the health literacy needed to navigate the healthcare system and complicated treatment regimens at the time. In the early DAA-era (2014-2016), we found that characteristics of those treated were older age (IRR: 1.05, 95% CI: 1.02, 1.07), current engagement in healthcare (IRR: 2.24, 95% CI: 1.34, 3.75), and having cirrhosis (IRR: 1.64, 95% CI: 1.16, 2.32), all of which are groups who would have been able to circumvent the early insurance restrictions enacted at that time. Finally, in the late DAA-era (2017-2019), participants who injected daily (IRR: 0.64, 95% CI: 0.39, 1.02) or who were HIV/HCV coinfected, but had a detectable HIV viral load (IRR: 0.35, 95% CI: 0.16, 0.76) had lower treatment rate than their counterparts. However, treatment uptake was better if a participant was already engaged in the healthcare system (IRR: 2.42, 95% CI: 1.56, 3.77). Our study found that treatment uptake has improved among many PWID, but it appears that treatment uptake is lower among those who are at highest risk of transmission or reinfection. While not surprising, this is concerning and signals that effective strategies to help engage these individuals in HCV care should be prioritized.

Strengths and Limitations

The strengths of our study stem from the fact that this research was nested in the ALIVE study. First, the ALIVE study's recruitment methods aim to achieve representation of the wider PWID community, including those who both are and are not engaged in the healthcare system or with harm reduction services.[8] The changing characteristics of the cohort over the past three decades further supports the representativeness of the study participants. It includes diverse representation across the spectrum and history of injection drug use in Baltimore City including older Black, urban PWID that were associated with the heroin and cocaine epidemics in the

1980s and 1990s, as well as, young, white suburban PWID, groups reflecting the current opioid epidemic. As one of the longest running community-based cohorts of PWID, there are three decades worth of rich data, which supported the longitudinal analyses completed here. Finally, we were able to use laboratory confirmation for HCV and HIV status, as well as, fibrosis stage, rather than self-report.

Our study also had several limitations. For Aim 1, some Census tracts had a small number of participants, which may limit the generalizability of this aim. While the small number of participants in Census tracts is a concern for mapping the crude viremia prevalence, we used Bayesian smoothing techniques to calculate the estimated prevalence of HCV viremia, adjusting for population size.[9,10] Furthermore, SaTScan is not impacted by a small number of cases because it considers different aggregations of data via the continuously moving window.[11,12] Another limitation is that we used reported residential addresses, which may not be where a person lives or sleeps, given the transient population. If so, our results may misrepresent the areas where treatment has penetrated in Baltimore. For Aim 2, we do not ask where participants were educated about HCV. We attempted to understand if education was happening before or after diagnosis by performing a sensitivity analysis, where we stratified by whether a participant was aware of their HCV infection prior to their baseline study visit or if they diagnosed through HCV testing done at ALIVE. This still limits out ability to draw conclusions about when a person was educated (i.e. at the time of testing) or by whom; however, this was not the primary focus of the aim. For Aim 3, HCV treatment, our outcome, was based on self-report and not confirmed with medical record review. As a result, there may have been underreporting of the number of people treated, particularly during the interferon-era when the treatment regimen was complicated. Also, self-reported HCV treatment was only asked to a subset of participants who stated that they were aware treatment was available and that they would agree to start treatment, when offered by an HCV provider. By contrast, in the DAA-era, all participants were

asked about HCV treatment. This skip pattern in the survey could have also contributed to undercounting the number of people who were treated in the interferon-era. However, since ALIVE studies in the interferon-era also reported that a small number of participants were treated during that time, it is unlikely to affect our findings.[13] Finally, there are also potential limitations given the nature of the study. For example, drug use, comorbidities, and healthcare utilization are self-reported. Given that these are sensitive topics, it is possible that participants may not accurately report the information. However, an earlier study in ALIVE showed good reliability in participant's self-reported answers.[14] Finally, it is possible that the ALIVE study population may not be representative of the larger PWID community. Not only do individuals need to be enrolled in the study and attend follow-up visits, but as a prospective study, there may be losses to follow-up. This is of particular concern for the participants that were recruited in the early cohorts and are now aging, and those who were HIV/HCV coinfected, as both groups are more likely to have experienced HCV-related morbidity or mortality that could result in them leaving the study. This would underestimate the participants with HCV viremia in Aim 1 and number of participants who were eligible for treatment but never treated in Aim 3. In both instances, it may overestimate the extent to which treatment uptake improved. However, results from both aims are consistent to findings in other studies.

Public Health Implications and Recommendations for Future Research

Our study demonstrated that treatment uptake among PWID has improved remarkably since the availability of DAAs. Furthermore, we found that treatment has penetrated even the most marginalized areas of Baltimore, Maryland. These results are encouraging and likely reflect the success and impact of many programs aimed at improving the health of PWID. For example, the Affordable Care Act expanded access to healthcare generally, but there were also programs specifically designed to improve treatment among PWID. Once treatment became simpler,

treatment was expanded into primary care and co-located at services utilized by PWID, like substance use treatment facilities that prescribe medication for opioid use disorder.[15–18] This not only helped to increase the number of providers that were able treat, but also helped make HCV treatment more accessible to people outside of the healthcare system. There have also been programs that successfully utilized patient navigation, peer support groups with treatment experienced PWID, and patient incentives.[19–24] Additionally, efforts were made to educate the providers, patients, and the public about DAAs. For instance, the CDC and pharmaceutical companies released formal education materials, PWID could also learn about DAAs through word-of-mouth, anywhere HCV testing is offered, at harm reduction services, healthcare offices or emergency departments. Our results stress the importance of not only continuing these efforts but also the need for future research to expand their reach.

However, given that transmission of HCV is ongoing, subgroups of PWID still fail to access HCV treatment for either initial infection or reinfection. Without improving treatment uptake among these groups, we will not achieve the HCV elimination goals. Furthermore, if left unaddressed, HCV-related mortality rates or comorbidities could increase in 20-30 years, similar to those who were infected in the 1980s and 1990s. We found the subgroup least likely to access HCV treatment were those who injected drugs daily, which is consistent with other studies in both the interferon-era and DAA-era.[3,13,25–28] There are structural, provider and individual-level barriers preventing even motivated PWID from being treated. For example, concerns with how to pay for treatment could impact both provider and patient willingness to be treated.[7,29–31] Motivated individuals may experience provider unwillingness due to stigma associated with active drug use or inconsistent engagement in healthcare.[7,30–33] Provider education can stress that cure rates are not affected by drug use, which may help assuage some reluctant providers but not all. Finally, most people do not experience HCV-related symptoms and may not prioritize treatment over more immediate concerns, like housing, employment, or food insecurity.[13,23,25]

Engaging this group of PWID will be difficult. Our findings stress the need for future studies to fully understand specific barriers that this group of PWID experience, which in turn can be used to develop innovative strategies to engage them.

HCV knowledge is a critical but modifiable factor that can improve treatment uptake among all PWID. Knowledge of the advancements of interferon-free, DAAs may motivate some PWID to be treated but misinformation regarding DAAs could be the reason some PWID choose not to initiate treatment. The most striking differences between DAAs and interferon-based therapies, are the higher cure rates, reduced pill burden, shorter duration of treatment, and minimal adverse events.[34–38] Our findings show that overall knowledge of HCV has improved in this population, but some residual misinformation about interferon-based therapies remains.[13] In particular, participants were aware that HCV is curable, but awareness the other key features of DAAs was mixed and particularly low among HCV negative PWID. This is consistent with another recent study among PWID in opioid treatment programs.[3] While we were unable to identify where PWID were educated about HCV and if treatment motivation varied by HCV knowledge level, it does warrant future investigation. This could be an important area of research because the quality of HCV education may vary between locations. Additionally, while most substance use treatment facilities that prescribe medication for opioid use disorder can educate consumers about HCV, there is evidence to show that many PWID do not access those HCV services.[23,39,40] Our findings did, however, identify HCV knowledge deficits that can be addressed more immediately to ensure that information about DAAs is relayed correctly.

Summary

Presently, HCV elimination is unachievable in the United States. The number of acute cases of HCV infections has increased for almost 10-years, with little indication that it is slowing.

Improving HCV treatment among PWID is key to decreasing HCV transmission. This study established knowledge in understanding how treatment uptake among PWID has changed from the interferon-era into direct acting antiviral (DAA) era. Additionally, we were able to provide insight into characteristics of PWID who are at-risk of not accessing HCV treatment now and potential barriers that may explain poor treatment uptake among some today. It highlights not only the progress that has been made to ensure equitable access to HCV treatment, but also raise awareness to where gaps may remain. Our study results can guide future research into the development of effective of strategies to improve treatment uptake and can also be used to direct allocation and placement of these interventions.

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Department of Epidemiology

Graduate Research Assistant
Worked closely with advisor, Shruti H Mehta, and co-advisor, Becky Genberg, to execute both research and organizational support for two large cohort studies. This has given me an appreciation for the implementation of an observational cohort study, including the benefits and challenges of using longitudinal and cross-sectional data, as well as potential difficulties like loss to follow-up.

- Created documentation of data harmonization procedures across the past 30 years of the ALIVE study. Started in 1988, ALIVE is the largest and longest running community-based cohort of PWID in the US. The ALIVE study is a

seminal study that not only contributed to our understanding of HIV, including natural history, risk factors and incidence, but also PWID and HCV.
- Created survey aimed to improved participant retention by ascertaining information regarding where participants spend time and services they use, in addition to residential mailing addresses
- Conducted a comparative analysis of participants enrolled in the ALIVE study (PI: Shruti Mehta) and Behavioral Surveillance Research (BeSure) Baltimore study (PI: Danielle German), a research study that uses respondent-driven sampling to measure HIV prevalence, health behaviors and access to services, among key populations, like PWID.

Teaching Assistant
Served as a teaching assistant (TA) for 20 classes. This includes lead TA, exam TA, and LiveTalk Instructor for the Principles of Epidemiology course to over 300 students, acted as a course coordinator to update fundamental epidemiology course, and teaching a basic epidemiology course to undergraduate states at Johns Hopkins University.

National Nursing Centers Consortium: Philadelphia, PA 2012-2016
National non-profit membership organization advancing nurse-managed health centers through programs, technical assistance and policy.

Public Health Project Manager
Lead a team to improve the dual HIV and HCV testing and linkage to care model and create systems level policy changes to support and improve care for HIV and HCV patients at 5 Philadelphia FQHCs. Most notably, the project won the Hepatitis Testing Innovation Contest in 2016, which highlighted HCV and HBV testing projects worldwide. The competition was a partnership by the WHO's Global Health Programme and Social Entrepreneurship of Sexual Health, in partnership with the European Association for the Study of the Liver (EASL). As a result, I presented at EASL's International Liver Congress in 2016. Additionally, the project is highlighted in the WHO's Guidelines on Hepatitis B and C Testing and published in the Centers for Disease Control and Prevention's (CDC) *Morbidity and Mortality Weekly Report* (*MMWR*) as a best practice for HCV testing. Other responsibilities included, providing on-going oversight and management of Philadelphia testing project, including supervision of program staff, reporting and project progress; overseeing capacity building of network providers to treat HCV and HIV in-house, project development and implementation; and spearheading teams to write manuscripts for peer-reviewed journals to disseminate lessons learned and project successes. Ensured that all project milestones were met according to prescribed timelines. Wrote grants to continue funding and expansion of program.
- Lead a team of external partners, including members from the CDC and Philadelphia Department of Public Health, to publish on project successes and lessons learned. Researchers included Drs. Deborah Holtzman and Jon Zibbell and Anne Moorman from the CDC; Helena Kwakwa MD and Kendra Viner PhD from the Philadelphia Department of Public Health; and former editor of The Lancet, Maja Zecevic PhD.
- Utilized data as mechanism for quality improvement.
- Communicated project successes by writing 4 manuscripts for scientific peer-reviewed publication and given 17 podium presentations at domestic and international conferences.
- Worked with health center staff to analyze workflow to increase the number of insured patients seen at clinics.
- Wrote HIV and HCV testing and treatment policies, automated project trainings.

- Served as direct liaison and provide data management and reporting to funding agencies.
- Developed and manage project budgets totaling $1,000,000.
- Continually modified EMR to support sustainability of testing, linkage to care, facilitate prior-authorization process for HCV treatment, and monitor patient treatment outcomes.
- Organized staff trainings for continued education units; update HIV and HCV related clinical best practices, treatment and prophylaxis; and educate primary care providers on culturally sensitive and proper results disclosure.
- Played an active role in network of community health centers, academic medical institutions and community organizations to improve earlier detection, linkage to care and treatment of people identified with HIV and chronic HCV infection.
- Recruited external partners to participate in expansion project to replicate the model into new NNCC member health centers.
- Collaborated with PHMC Communications to promote project and NNCC Technical Assistance department to provide technical assistance for member health centers implementing routine HIV and HCV testing as a standard of care.
- Created longitudinal dataset of HCV tested patients using electronic medical records. Variables included those reported to funders, like demographics and linkage to care results, as well as co-morbidities, laboratory test results, risk factors, reasons patients chose not to seek care, and treatment outcomes. This was used to improve quality of care of HIV and HCV infected patients and conduct clinical research.
- Worked with commercial laboratories to create testing algorithms to best serve community health center patient population.

Public Health Project Coordinator/Hepatitis C Testing Project Coordinator
Built and managed an innovative and successful dual HIV and HCV testing and linkage to care model in 5 Philadelphia FQHCs by writing standard of care and implementation protocols to integrate into practice. Collaborated with health centers to exceed programmatic goals for testing grants funded by the CDC and Gilead Sciences, Inc.

- Reported monthly data to funders and HCV-positive patients to HCV surveillance at the Philadelphia Department of Public Health.
- Tracked HIV and HCV patients through continuum of care including diagnosis, results notification, referral to specialists, attending specialist appointment and treatment.
- Developed project implementation timeline for both testing programs to ensure enough time to meet project goals.
- Created audit tools and quality measures to ensure high quality patient care.
- Negotiated with commercial laboratories to perform tests on uninsured patients.
- Tracked patient progression through continuum of care and managed data to ensure project progress.
- Supervised Linkage to Care Coordinator.
- Wrote and managed project budgets totaling $700,000.
- Raised $450,000 in grant funds.
- Cleaned and uploaded monthly reporting variables, managed data.
- Organized clinic staff trainings and education sessions.
- Consistently met contract, grant writing and administrative project requirements and timelines.

Elite Rower: Philadelphia, PA 2005-2008
Professional training for World & US Rowing competitions.

Ad hoc reviewer for Clinical Infectious Diseases, Public Health Reports, International Journal of Drug Policy, and BMJ Open
Proficiency: Stata, ArcGIS, SaTScan, GeoDa
Doctoral funding: F31 NSRA pre-doctoral fellowship (2020); pre-doctoral funding provided by NIH T32AI102623 (2017-2019), HIV training grant; Bloomberg American Health Initiative (BAHI) grant for Legionella cluster detection in Maryland (2020)

RELATED EXPERIENCE

The Rothman Institute: Philadelphia, PA 2008-2010
Assistant Research Fellow, Joint Research

PHMC Health Services Intern: Philadelphia, PA 2009-2013
Transferred all paper medical records to the EMR and worked with a Ryan White funded health center to improve Ryan Write reporting indicators.

COMMITTEES

Co-chair, Doctoral Student Council, 2017-2019
Founding co-lead, student group of ALIVE trainees, 2017-2020
Member of Johns Hopkins' Surveillance, Outbreak Response Team. Team Lead for Data Visualization Group, 2017-present
Baltimore City Health Department and Maryland Department of Health, 2017-present
Member of Maryland Hepatitis Coalition, 2017
Advisor, Gilead Medical Affairs Advisory Program, 2014
Member of Hepatitis C Advisory Committee, National Healthcare for the Homeless Council, 2014

AFFILIATIONS

Hepatitis C Alliances of Philadelphia (HepCAP); Young Friends of Students Run Philly Style, American Public Health Association (2014-2015), Young Leaders of Project HOME

PUBLICATIONS

- Coyle C, Moorman AM, Bartholomew T, Klein G, Kwakwa H, Mehta SH, Holtzman D. The HCV care continuum: linkage to HCV care and treatment among patients at an urban health network, Philadelphia, PA. Hepatology; 2019.
- Coyle C, Viner K, Hughes E, Kwakwa H, Zibbell JA, Vellozzi C, Holtzman D. Identification and linkage-to-care of HCV-infected persons in five health centers, Philadelphia, PA 2012-2014. Morbidity and Mortality Weekly Report; May 8, 2015.
- Coyle C, Kwakwa H. Dual-routine HCV and HIV testing: seroprevalence and linkage to care in four community health centers in Philadelphia, PA. Public Health Reports Supplement; January/February 2016.
- Coyle C, Kwakwa H, Viner K. Integrating routine HCV testing in primary care: lessons learned from five federally qualified health centers in Philadelphia, PA. Public Health Reports Supplement; April/May 2016.

- Kwakwa H, Bessias S, Sturgis D, Wahome R, Coyle C, Flanigan T. Attitudes towards HIV pre-exposure prophylaxis in a United States urban clinic population. AIDS and Behavior; July 2016.
- Huang R, Barrazueta G, Ong A, Orozco F, Jafari M, Coyle C, Austin M. Revision total knee arthroplasty using metaphyseal sleeves at short-term follow-up. Orthopedics; September 2014
- Jafari SM, Bender B, Coyle C, Parvizi J, Sharkey P, Hozack WJ. Do tantalum and titanium cups show similar results in revision hip arthroplasty? Clinical Orthopaedics and Related Research; February 2010.
- Jafari SM, Coyle C, Mortazavi SMJ, Sharkey P, Parvizi J. Revision total hip arthroplasty: infection is the major cause of failure. Clinical Orthopaedics and Related Research; September 2009.

HIV AND HCV PODIUM PRESENTATIONS AND WEBINARS

- Coyle C, Kwakwa H. An Innovative Model to Integrate HCV Testing and Linkage to Care in Five Federally Qualified Health Centers in Philadelphia, PA. European Association for the Study of the Liver, The International Liver Congress. Barcelona, Spain. April 2016.
- Coyle C, Kwakwa H. An Integrated HCV Testing Model as a Method to Improve Identification and Linkage to Care in a Network of Com unity Health Centers in Philadelphia, PA. International Conference on Viral Hepatitis, London, England. September 25-26, 2015.
- Coyle C. Dual Routine HCV and HIV Testing as a Method to Improve Detection and Linkage to Care of HCV and HIV-Positive Patients at a Network of Community Health Centers in Philadelphia, PA. Summit on HCV and HIV Diagnosis, Prevention and Access to Care, Arlington VA. June 2015.
- Coyle, C. An Advanced Model to Routinize Hepatitis C Testing and Linkage to Care for Homeless Patients in Philadelphia, Pennsylvania. National Healthcare for the Homeless Council Conference and Symposium, Washington DC. May 2015 (workshop).
- Panel Presentation: One Stop Testing Shops: Lessons from Local Integrated HIV and Hep C Testing Models. Prevention Summit. Philadelphia, Pennsylvania. June 18, 2014.
- Panel Presentation: Successful Strategies and Barriers to Reimbursement for Routine HIV Tests. Prevention Summit. Philadelphia, Pennsylvania. June 18, 2014.
- Panel Presentation: Prevention Summit. Lessons Learned Implementing Routing HIV Screening in FQHCs. Philadelphia, Pennsylvania. June 18, 2014.
- Coyle C. Linkage to Care Coordinator as an Intervention to Improve Care. HepTLC Webinar for HCV (CHC) Grantees—Overcoming Barriers in HepTLC Data. May 12, 2014.
- Coyle, C. The Philadelphia Hepatitis C Testing Project: A Replicable and Scalable Model for Routine Hepatitis C in Five Federally Qualified Health Centers. Community Health Partners for Sustainability New Models of Care for Hepatitis C Webinar. May 6, 2014.
- Coyle C. The Philadelphia Hepatitis C Testing Project: A Replicable and Scalable Model for Routine Hepatitis C in Five Federally Qualified Health Centers. The Centers for Disease Control and Prevention, Atlanta, Georgia. January 27-28, 2014.

HIV AND HCV RELATED POSTER EXHIBITS

- Coyle C, Moorman AM, Bartholomew T, Klein G, Kwakwa H, Mehta SH, Holtzman The HCV care continuum: linkage to HCV care and treatment among patients at an urban health

network, Philadelphia, PA. American Association for the Study of Liver Diseases, The Liver Meeting. Washington DC. November 17-19, 2017.

- Coyle C, Kwakwa H Integrated Routine HIV Testing: Implementation, Outcomes and Lessons Learned from Four Federally Qualified Health Centers in Philadelphia, Pennsylvania, 2013-2015. National Conference on HIV Prevention, Atlanta GA. December 6, 2015.
- Coyle C. Electronic Medical Record Modifications to Support Integrated Routine HCV and HIV Screening and Linkage to Care in Five Community Health Centers in Philadelphia, PA. Summit on HCV and HIV Diagnosis, Prevention and Access to Care, Arlington VA. June 2015.
- Coyle C, Klein G, Kwakwa H. An Innovative and Scalable Model to Routinize HCV Testing and Linkage to Care in Five Federally Qualified Health Centers. American Association for the Study of Liver Diseases, The Liver Meeting. Boston, Massachusetts. November 9-10, 2014

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